FOOD AND DRUG ADMINISTRATION

84TH MEETING OF THE

CARDIOVASCULAR AND RENAL DRUGS

ADVISORY COMMITTEE

Friday, April 10, 1998

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TABLE OF CONTENTS

P R O C E E D I N G S [8:30 a.m.]

DR. PACKER: This is the second day of the 84th meeting of the Cardiovascular and Renal Drugs Advisory Committee. We will begin by asking Joan to read any administrative matters that are pertinent to today's meeting.

Agenda Item: Conflict of Interest Statement

MS. STANDAERT: This is the Conflict of interest statement. The following announcement addresses the issue of Conflict of Interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and information provided by the participants the agency has determined that all reported interests in firms regulated by the Center for Drug Evaluation and Research present no potential for a conflict of interest at this meeting with the following exception. Waivers have been granted to Dr. Milton Packer, Dr. Marvin Konstam, Dr. JoAnn Lindenfeld, Dr. Lemuel Moye, and Dr. Dan Roden which will permit them to participate in all official matters concerning Aggrastat.

A copy of the waiver statements may be obtained by submitting a written request to FDA's Freedom of Information Office, Room 12A-30 of the Parklawn Building. Dr. Robert Califf and Dr. Cindy Grines are excluded from participation

in all matters concerning Aggrastat.

In addition, we would like to discuss that Dr. Konstam is listed as a sub-investigator on the RESTORE study of Aggrastat. Dr. Konstam never enrolled a patient nor did he have any involvement whatsoever in this study.

In the past, Dr. Thadani has studied Integralin and Lovanox, competing products to Aggrastat. Since Dr. Thadani has no continuing interest in these products, he may participate in all official matters concerning Aggrastat.

We would also like to note for the record that Dr. Packer and Dr. Borer have interests which do not constitute financial interest in the particular matter within the meaning of 18 USC208(a) but which could create an appearance of a conflict. The agency has determined, notwithstanding these interests, that the interest of the government in their participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Packer and Dr. Borer may participate in all official matters concerning Aggrastat.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for

the record. With respect to all other participants, we ask in the interest of fairness that they may address any current or previous financial involvement with any firm whose products they may wish to comment upon. That concludes the conflict of interest statement for April 10, 1998.

DR. PACKER: Thank you very much, Joan. We normally reserve time for public comment at this time. If there is any public comment, please come to one of the microphones. There not being any public comment, we will proceed with a presentation of Tirofiban.

The proposed indication is for the treatment of patients with unstable angina or non-Q-wave myocardial infarction. The sponsor is Merck Research Laboratories. Please proceed.

Agenda Item: NDA's 20-912 and 20-913, Aggrastat (Tirofiban hydrochloride intravenous injection, Merck Research Laboratories), indicated in combination with heparin, to prevent cardiac ischemic events in patients with unstable angina or non-Q-wave myocardial infarction, including those patients in whom coronary angiography and angioplasty/atherectomy are clinically indicated - Introduction

DR. BELL: Good morning, Mr. Chairman, and members of the Advisory Committee, FDA, ladies and gentleman. My

name is Larry Bell. I would like to provide some brief introductory remarks before we present the results of our clinical development program.

Before beginning, I actually would like to than the Advisory Committee, the FDA for the opportunity to present our results which support the new drug application for Aggrastat, Merck's trade name for Tirofiban hydrochloride.

Tirofiban hydrochloride is a potent non-peptide inhibitor of the platelet glycoprotein IIb/IIIa receptor. It also is noted for having high specificity for the receptor and has a short half-life of approximately two hours, and is intended for use as an intravenous agent. In addition, by blocking fibrinogen binding to the IIb/IIIa receptor, Tirofiban prevents cross-linking of platelets which is a basis of platelet aggregation.

Tirofiban, therefore, was developed for use in clinical settings in which rapid inhibition of platelet aggregation is important to prevent thrombus formation and propagation that could lead to subsequent clinical events.

In the development of Tirofiban, Merck Research Laboratories has carried out a comprehensive clinical program that will be summarized today to explore the efficacy and safety of the compound. Of note, before embarking on the individual phase III clinical trials,

appropriate phase II dose finding studies with Tirofiban either alone or combined with heparin were conducted.

As will be discussed during the presentation of the results of these trials, these studies were designed to specifically target a dose of Tirofiban that, while achieving the most consistent inhibition of platelet aggregation across the study population was also associated with an acceptable bleeding profile.

The phase III program consisted of three large clinical endpoint trials encompassing more than 7,200 patients. The program focused on acute coronary ischemic syndromes and, in particular, unstable angina pectoris and non-Q-wave myocardial infarction in which rupture of the atherosclerotic plaque in the coronary artery leads to platelet aggregation and thrombus.

The advisory committee members have received the background package from Merck that summarizes this large body of information which we believe demonstrates Tirofiban as efficacious and safe and supports the proposed indication that we are seeking.

As noted in the indication that appears on this slide, we believe the information that has been summarized for you on this background package, as well as the information that will be discussed on today's meeting supports the use of Tirofiban in combination with heparin to

cardiac ischemic events in patients with unstable angina, non-Q-wave myocardial infarction, including those patients in whom coronary angiography and angioplasty or atherectomy are clinically indicated.

Following this introduction, Dr. Rick Sax, leader of the development program for Aggrastat at Merck will provide you with a comprehensive review of our development program as well as concluding remarks.

In addition to our speakers, Merck Research Laboratories has also brought the consultants today that appear on this slide. These experts are available to facilitate the advisory committee's discussion, as well as deliberations. After Dr. Sax completes his presentation, either he or the consultants would be happy to address any questions that the committee may have.

With that I would like to turn the podium over to Dr. Sax.

Agenda Item: Clinical Efficacy and Safety

DR. SAX: Dr. Packer, members of the committee, members of the FDA and ladies and gentlemen. Tirofiban hydrochloride is a short-acting, non-peptide inhibitor of platelet glycoprotein IIb/IIIa. It was developed for rapid intravenous use in acute coronary ischemic syndromes in which platelet aggregation contributes to thrombosis and subsequent morbidity.

The molecule was designed to be a potent, highly-specific inhibitor of the binding of fibrinogen to glycoprotein IIb/IIIa. By fitting precisely into the receptor and blocking fibrinogen binding, Tirofiban prevents the cross-linking of the platelets and thus prevents platelet aggregation.

The clinical program for Tirofiban focused on acute coronary ischemic syndromes in which the disruption of atherosclerotic plaque leads to platelet aggregation and thrombosis. Notice that plaque injury also leads to thrombin generation and fibrin generation which contributes to the thrombotic process. Thrombin generation is also the most potent agonist of platelet aggregation. Thus, current pharmacotherapy for acute coronary ischemic syndromes uses agents, aspirin and heparin to block both aspects of arterial clotting, platelets and thrombin.

These aspects of the clotting system are what leads to thrombosis and the subsequent cardiac ischemic events such as unstable angina, myocardial infarction and cardiac ischemic death.

Tirofiban is a much more potent inhibitor of platelet aggregation than aspirin and thus the program hypothesis was that added blockade of platelet aggregation would lead to improve clinical outcomes.

The development of a compound for patients with

unstable angina non-Q-wave MI must be incorporated into the overall clinical management of this syndrome. This involves an initial period of medical stabilization. Following this, the patients often undergo angiography and, based on the findings on the angiogram are triaged to ongoing medical therapy, coronary artery bypass surgery or percutaneous intervention.

A highly-effective anti-platelet agent, combined with a highly-effective anti-thrombin such as heparin thus has two opportunities to potentially benefit patients in the course of the management of this syndrome. The combined therapy could contribute to medical stabilization of patients by preventing ongoing thrombus formation and clot propagation allowing the body's intrinsic fibrinolytic system to dissolve the clot and passivate the unstable plaque.

Second, at the time of re-injury of the unstable plaque through coronary intervention, a potent anti-platelet agent could prevent subsequent complications that are related to thrombosis such as abrupt closure following the procedure.

A drug that prevents platelet aggregation thus could potentially have an effect both on the initial medical management of patients and after procedures in patients with unstable angina and non-Q-wave infarction.

Now, at the inception of the program for Tirofiban, it was unknown how potent platelet blockade could benefit the different stages of the management of this syndrome. We, therefore, undertook a clinical program that was structured to define the benefits of Tirofiban across the different aspects of treatment for this syndrome. The program focused first on the medical stabilization period with a study called the PRISM Study. In this study Tirofiban was examined for medical stabilization in a period of time that did not involve concomitant procedures.

A second trial, PRISM-PLUS, also looked at the medical stabilization period. But, unlike the PRISM study, the study drug was continued through angiography and then through coronary angioplasty if that was clinically indicated.

Lastly, a third trial, the RESTORE trial, studied the use of Tirofiban later in the treatment paradigm when initiated at the time of angioplasty. This study thus focused on the component of unstable angina involved with angioplasty without pretreatment before the angioplasty.

Together these studies, PRISM, PRISM-PLUS, and RESTORE are designed to demonstrate the overall benefit of Tirofiban as well as elucidate the benefit of Tirofiban on each of the stages of the management of unstable angina, non-Q-wave infarction. Over the course of the next 45

minutes, I will be discussing the key findings of these three trials which assess the complementary and overlapping aspects of the treatment on unstable angina, non-Q-wave MI. Taken together, these trials provide consistent evidence supporting the use of Tirofiban for the medical management of unstable angina MI and its effects on percutaneous coronary interventions.

As I will discuss, in each of these trials, Tirofiban reduces early cardiac ischemic events. It was in fact, however, the combined use of Tirofiban and heparin as part of the overall treatment approach that produced the most potent, and robust, and durable results.

I will then review the safety of the compound which relates back to our early dose finding studies and, in particular, the selection of the dose when given in combination with heparin.

So, before I turn to the description of the individual trials, I would like to spend a few minutes just describing the rationale for dose selection.

We targeted in this program achieving greater than 70 percent inhibition of platelet aggregation by ex vivo platelet aggregometry in our dose finding studies based on animal data and our clinical experience with a previous GP IIb/III inhibitor. These data suggested that if at least 70 percent inhibition could be achieved there would be a

reduction in subsequent thrombosis and related events. We also wanted to be sure that this degree of inhibition could be consistently achieved across the populations and that the dose would have an acceptable bleeding profile both by bleeding times and a lower rate of discontinuations due to bleeding.

The phase II studies were thus designed to try to define the optimal dose of Tirofiban both without and with heparin that would have an acceptable pharmacodynamic profile and an acceptable safety profile.

Now, shown here are the data from the first dose finding study with Tirofiban which was conducted without heparin. Most patients in this study, as was true in the phase III program as well, received concomitant aspirin.

There were three panels studied. Each study, each panel involved a 30-minute loading infusion followed by a 47 and a half hour maintenance infusion. As you can see across the various panels studied, each regimen that we studied achieved the targeted inhibition of at least 70 percent IPA-induced inhibition of platelet aggregation. But it was at the highest dose, with a maintenance infusion of 0.15 micrograms per kilogram per minute that we achieved the most consistent inhibition with over 95 percent of patients achieving this targeted level of inhibition.

The bleeding times were all within an acceptable

range. The highest regimen achieved bleeding times of 14 to 20 minutes. I would just point out that in this population, patients on aspirin have a bleeding time in the range of six to eight minutes. The bleeding profile associated with this regimen was quite good and there were no discontinuations due to bleeding and no major bleeding.

Thus, this dose of the 0.6 microgram per kilogram per minute, 30-minute loading infusion, followed by a maintenance infusion of 0.15 micrograms per kilogram per minute was chosen for phase III studies in which Tirofiban was going to be administered without heparin.

Now, shown here is the same dose that I have just discussed for use without heparin, and the comparable pharmacodynamic data for studies when Tirofiban was administered with heparin. As you can see, the lower infusion regimen of 0.1 micrograms per kilogram per minute as a maintenance infusion regimen achieved a pharmacodynamic profile that was quite similar to the regimen of 0.15 without heparin's comparable median bleeding times. And in fact here 93 percent of the population achieved the targeted level of greater than 70 percent.

Notice also that the bleeding times here were comparable to this regimen without heparin, 14 to 20 minutes.

When we use the higher regimen of 0.15 with

heparin, the bleeding times were higher. In fact, it appeared that heparin increased the bleeding time. So with this regimen, bleeding times were in the range of 26 to 30 minutes. And, in fact, about 60 percent of patients at some time point had a bleeding time that was in excess of 30 minutes.

This dose with heparin was also accompanied by a higher rate of bleeding than the other regimens that we studied. In fact, with this dose of 0.15 with heparin, 13.5 percent of patients in the phase II program had to discontinue due to bleeding adverse events.

Therefore, we decided that when the drug was to be used in combination with heparin, we would use the lower regimen, a loading infusion of 0.4 micrograms per kilogram per minute, followed by a maintenance infusion of 0.1 micrograms per kilogram per minute, again, when Tirofiban was used in combination with heparin.

Note, again, that from a pharmacodynamic perspective of platelet inhibition, namely median bleeding time -- I am sorry, median platelet aggregation or median bleeding times, the two regimens without -- this regimen without heparin and this regimen with heparin were quite comparable. However, one needs to remember that adding an anti-thrombin to an anti-platelet agent leads to an additional effect on the coagulation system which may

contribute both to clinical benefit but also an increased risk of bleeding. This, of course, would need to be studied formally in the phase III trials.

With this in mind, let me now turn to the phase III trials which study Tirofiban for unstable angina non-Q-wave MI.

DR. PACKER: Dr. Sax, before going forward, let me just ask if anyone on the committee has any questions about the dose finding studies or anything about the pharmacology of the drug or the physiology of the disease before we go on to the three major clinical trials.

DR. LIPICKY: I have one. Do you happen to have a slide that shows the time course of either platelet agglutination inhibition or plasma concentrations at those two doses?

DR. SAX: If you would like to see a slide, Dr. Lipicky, we could show that. But I can tell you that platelet inhibition was quite rapid. At the end of the 30-minute loading infusion we achieved the levels of platelet inhibition as well as the plasma concentrations that were sustained throughout the infusion.

So, at 30 minutes, we were at 90 percent inhibited, and that was well-maintained for the plasma concentrations that were also at the levels that we --

DR. LIPICKY: No. It is not that I doubt that. I

would just like to see the slide. You do not have to bring it out now, but just sort of have it at some time.

DR. PACKER: Udho, why don't you -- while they are finding the slide, do you have a question?

DR. THADANI: Yes, Dr. Sax, while they are doing that, one of the issues --

DR. SAX: May I have slide A29 please?

DR. PACKER: We have got to hold off for a second.

DR. THADANI: Yes, okay.

DR. SAX: This is actually post-bolus, Dr. Lipicky. You will see that these are the three regimens that were studied. This happens to be a PTCA study where we actually used a bolus infusion rather than a loading infusion. But the bolus infusion and the loading infusion achieved quite comparable levels. But you can see that platelet inhibition was obtained within three minutes of giving the bolus infusion, this being a five microgram per kilogram bolus, this being a 10 microgram, these both being 10 microgram per kilogram boluses. And then these were maintained throughout the period.

DR. LIPICKY: I am sorry. I meant the bolus followed by the infusion and what that time course looks like.

DR. SAX: Actually, could I have that slide again? Again, you can see the bolus here. This is the bolus, and

then this was a 16 to 24-your infusion. The levels were well maintained over that period of time.

DR. LIPICKY: But all you see is the post-bolus and then the steady state and you do not see in between.

DR. SAX: We do not have measurements from the end of the bolus infusion through the first 24 hours.

DR. LIPICKY: I see. Okay. Thank you.

DR. PACKER: Udho.

DR. THADANI: Normally in clinical practice the bleeding time is a very poor marker for bleeding. And yet in your data you showed in the small numbers. When the bleeding time was high you said there was a -- bleeding rate. Have you done a correlation between the bleeding times and actually the bleeding complications in these small pilot studies?

DR. SAX: No. In fact, your comment is exactly correct. The bleeding time correlates as correlated in other studies and our study very poorly as a predictor of bleeding. The bleeding time here was used more as an index of platelet aggregation, kind of as a check against the platelet aggregometry. But we did not use the bleeding time as a predictor for bleeding. It does correlate poorly.

At the highest dose of 0.15, in combination with heparin, which had the highest bleeding times also, it turned out that there was a high rate of discontinuations

due to bleeding, but we did not find a direct correlation between bleeding times and bleeding event rates.

DR. THADANI: Another question which may be relevant. Were any of these subjects on nonsteroidals?

DR. SAX: There were patients on nonsteroidals who came in on nonsteroidals. But at least in the phase II programs we excluded nonsteroidals during the study period.

DR. PACKER: Okay.

DR. SAX: Okay. With this in mind, let me turn now back to the two unstable angina trials that were used to study Tirofiban for the management of unstable angina non-Q-wave infarction.

These two trials respectively were called PRISM and PRISM-PLUS as I had mentioned. PRISM focused exclusively on the medical stabilization period with a 48-hour infusion during which time procedures were not to be performed unless the patient reached a clinical endpoint. PRISM also studied Tirofiban alone without heparin and it thus represents a pure test of the utility of an antiplatelet agent for the initial management of this syndrome.

PRISM-PLUS studied the medical stabilization period as well, but then the drug was allowed to be continued through angiography and through angioplasty if that was clinically indicated.

PRISM-PLUS also studied Tirofiban both with and without heparin. Again, the dose that we used for Tirofiban with heparin was designed to both inhibit platelet aggregation and, of course, with heparin inhibit the thrombin-mediated limb of a clotting system in a way that we had hoped would not compromise safety.

Thus, PRISM is essentially the study that was designed to show that the drug had activity. PRISM-PLUS, both with the use with and without heparin and as part of this overall management strategy, was the study that was designed to attempt to define the optimal use of the drug.

Both trials enrolled comparable populations of patients with symptoms of rest or accelerating chest pain. In PRISM, however, patients could be enrolled within 24 hours of the onset of their last symptoms of chest pain. In PRISM-PLUS, patients had to be enrolled within 12 hours. So PRISM-PLUS, by this criteria alone, represents a somewhat high-risk population.

In both trials, patients could enter the trial if they had electrocardiographic evidence of ischemia or if they had evidence of elevated cardiac enzymes at the time of their clinical presentation. However, in the PRISM trial, patients could also enter if they had a history of coronary artery disease as defined by a history of a previous myocardial infarction, previous bypass surgery, previous

angioplasty or a positive stress test. Thus, based on these inclusion criteria, PRISM enrolled a somewhat broader but also lower-risk population than PRISM-PLUS.

The inclusion criteria are reflected in the clinical presentations of patients in the respective trials. As you can see, PRISM had a somewhat lower rate of patients with documented ischemia or elevated enzymes than PRISM-PLUS, where these criteria were mandatory to get into the trial.

As you can also see, there was a somewhat lower rate of non-QA myocardial infarctions in the prism trial, and a higher rate of unstable angina, as opposed to prism plus where almost have of the population was found to have a non-Q-wave MI. Otherwise, the overall baseline demographics of the two trials are quite comparable.

As you can see from this slide, the populations were similar and, in fact, similar to what one would expect for patients who present with this syndrome. The mean age of the population was just over 60 years. About a third of the population was female. Most of the population was Caucasian, with about five percent Blacks. About half of the population had a previous history of infarction. A little over half had a history of hypertension. Almost half had hypercholesterolemia, and about a fifth of the population were diabetics. The diabetics, in particular,

had been particularly resistant to treatment, especially in the setting of procedures.

So, let me turn now to the specifics of the PRISM trial, which is the first trial we conducted for the management of unstable angina non-Q-wave infarction. This trial enrolled over 3,200 patients and focused on the question of whether Tirofiban alone could be used to medically stabilize patients.

The primary hypothesis of the trial was in patients with unstable angina, non-Q-wave infarction, Tirofiban will reduce the composite endpoint of refractory ischemia, new myocardial infarction and death compared with heparin at 48 hours.

Refractory ischemia was defined as a failure of medical management with ongoing severe or repetitive anginal symptoms with objective evidence of ischemia through what the physician determined was optimal medical management.

Myocardial infarction also required symptoms and objective verification of infarction. Death from any cause was counted. All endpoint events were investigator-identified and were adjudicated by an endpoint committee blinded to the treatment group.

Thus, in this trial, Tirofiban was randomized against an active control, heparin, representing the standard of care for medical stabilization of patients at

the time that the trial was conducted. Note, again, that all patients in this trial, as in the other phase three trials, received concomitant aspirin.

This trial, the PRISM trial, as I have mentioned, was thus a rigorous test of the effect of Tirofiban as heparin was not concomitantly administered. Only the platelet component of thrombosis was inhibited.

The overall design of the trial was illustrated here. There was a 48-hour drug infusion period during which procedures were not to be performed unless the patient reached a clinical endpoint. The primary endpoint of the trial was therefore chosen at the end of the drug infusion at 48 hours. We also followed patients for seven days, representing the hospital course. This was the secondary endpoint. And we did have longer-term follow-up, out to 30 days, as a pre-specified supportive analysis. At the seven-day time point and the 30-day time point, re-admissions for unstable angina were also counted in addition to the other components I have mentioned of a primary endpoint.

The trial was conducted under the auspices of an independent data safety monitoring board. There were two planned interim efficacy analyses. As a result of this the critical P value to declare the trial significant was set at 0.047.

There was one sample size readjustment during the

course of the trial. The original plan sample size of 1,000 patients per group was increased to 1,550 patients per group by the steering committee due to a low blinded pooled group event rate.

This trial was also -- all analyses were performed on an intention to treat basis and, therefore, all randomized patients were included in the analyses.

This slide shows the time-to-event curve for the primary endpoint for prism, from the time of randomization to 48 hours at the end of the drug infusion. The curves represent the percent of patients experiencing the composite endpoint of refractory ischemia, new myocardial infarction, or death.

As you can see, curve separated at 24 hours so that at the end of the 48-hour infusion period, the event rate in the heparin control group of 5.6 percent was reduced to 3.8 percent with Tirofiban.

This reduction from 5.6 percent in the heparin group to 3.8 percent with Tirofiban, represents a 34 percent odds reduction in cardiac ischemic events, and was statistically significant with a P value of 0.014. As you can see, refractory ischemia was reduced from 5.3 percent to 3.5 percent, and myocardial infarctions at 48 hours were reduced from 1.4 percent to 0.9 (sic) for the percent. These also individually represent about a one-third odds

reduction and are consistent with the overall findings for the composite endpoint. Deaths representing six deaths in the Tirofiban group and four deaths in the heparin group were infrequent at this time point. A statistical test showed no significant heterogeneity among components.

This slide shows the consistency of effect across the major demographic subgroups at the primary endpoint plotted on a log scale of odds ratios. As you can see, there was a consistent drug effect across the groups of age, gender, presentation of unstable angina or non-Q-wave MI for diabetics, patients with antecedent heparin, antecedent aspirin, and U.S. or non-U.S. countries. All groups had a benefit from Tirofiban.

Now, after a completion of the study at 48 hours, patients were treated as determined by local practice which could include open-labeled heparin, angiography, and angioplasty. But all of these were off-drug and not controlled in an way in the protocol.

Shown here are the secondary endpoints at seven days and the supportive endpoint at 30 days for the composite endpoint. There continue to be a nominal reduction of events for Tirofiban representing about a 10 percent reduction in the odds ratios. But neither of these at seven days or 30 days reached statistical significance.

So to just briefly summarize the PRISM trial. In

patients with unstable angina non-Q-wave infarction, Tirofiban alone without heparin further reduces acute cardiac ischemic events during a 48-hour medical stabilization period compared to heparin. The results are consistent across the subgroups at the primary endpoint and the trial thus provides strong evidence that the drug alone is effective for early medical stabilization.

DR. PACKER: Can we pause for a moment and see if the committee has any specific questions about the PRISM trial? I will ask Dan Roden, the primary reviewer, to lead off the discussion.

Agenda Item: Questions and Answers

DR. RODEN: yes. I am interested in knowing a little bit more about the major element of the composite endpoint, the recurrent ischemic events. How were they judged, and was there some sort of oversight in terms of reviewing them?

DR. SAX: Yes. You are speaking specifically of refractory ischemia?

DR. RODEN: The RICs.

DR. SAX: Yes. Refractory ischemia was identified by the investigators. Again, there had to be objective evidence of symptoms, electrocardiographic changes, and the investigator had to make a determination that the patient was on optimal medical therapy. The protocol gave some

guidelines as to what constituted optimal medical therapy, namely, that patients had to be on nitrates, and beta-blockers, or a calcium channel blocker which could be titrated to heart rate and blood pressure, suggesting that the patient had been optimally placed on these medications.

That information was then submitted along with a narrative to an endpoint committee. The endpoint committee consisted of three expert cardiologists with active clinical practices especially in acute coronary ischemic syndromes. That evidence was then evaluated by the endpoint committee and adjudicated as being refractory to medical management or not being refractory to medical management. So this was investigator-identified endpoints reviewed by three expert cardiologists. And the opinion of the endpoint committee constituted the final adjudication of the endpoint.

DR. PACKER: Just to clarify that for a moment. On the adjudication process was of the endpoints reported by investigators. The adjudication committee did not review all of the patients in the trial in terms of their overall clinical status?

DR. SAX: The endpoints were reviewed -- were identified by the investigators and were submitted to the endpoint committee. The endpoint committee had the discretion of changing the endpoints or even potentially identifying new endpoints. But it was the endpoints

identified by the investigators that were reviewed.

DR. PACKER: How many times was there an agreement or a disagreement between the endpoints submitted by the investigator and the endpoints deemed to meet an endpoint by the adjudication process? As you notice this has arisen in other trials of antiplatelet drugs.

DR. SAX: Yes. In general, the endpoint committee adjudicated yes or no. And so what we found was that the endpoint committee in fact rejected a certain percentage of the endpoints identified by the investigators. So, in fact, the endpoint committee, to some sense, if you could look at it this way, was decreasing the noise submitted by the investigators. A lot of that had to do with a lack of careful electrocardiographic documentation. The endpoint committee tended to be fairly rigorous about insisting on ischemia. So there was a reduction in events.

DR. PACKER: Did the adjudication process follow the judgment of the three individuals on the committee or did they have pre-specified, written-down rules as to what they judged to be repetitive or refractory?

The reason for asking is because repetitive is subjective. Many of the words used to describe refractory ischemia represents subjective terms. Although one could think that three experienced cardiologists might agree or disagree, the question is did they actually have written-

down rules that guided this process?

DR. SAX: Yes. There was a formal endpoint committee manual which was derived from the protocol and was put together with the assistance of the steering committee and guidance from the steering committee as well as involvement of the endpoint committee. However, we recognize that one could not follow specific rules for the adjudication of every case. So these were essentially guidelines. I think what you have to recognize is that the patients had symptoms. That is objective. They had to have documented ischemia. That is fairly objective. Where the subjectivity might come in is what constitutes optimal medical therapy. Again, this relies somewhat on the judgment of the cardiologists, both the investigator submitting the case report form and then the three expert cardiologists with the committee.

If I could add one other point? This committee, the PRISM committee required a consensus to vote. In other words, there were three members. But any cases where there was disagreement, all three members had to teleconference and agree. So that is a fairly rigorous adjudication process for this particular study.

DR. PACKER: Not to belabor this point. But this is the endpoint which drives the result. So it is important for the committee to understand how this endpoint was

processed. How is repetitive defined?

DR. SAX: The protocol gave guidelines that repetitive would be defined as at least two episodes of 10 minutes of duration occurring within an hour. That was the guideline for repetitive.

DR. PACKER: Was the committee privy to any other data aside from the clinical history provided to them about the ischemic events reported by the investigators?

DR. SAX: Yes. Angina was very meticulously documented. The committee received the case report forms dealing with the endpoint material which included the anginal episodes that occurred at all times during the trial, the duration of the anginal episodes, all cardiac enzymes, all electrocardiograms, and all medications, and the heart rates and blood pressure at the time of the episode. That information was all provided.

In addition, the committee was also privy to the angiographic findings, if any angiograms were performed. And the committee also was given the overall clinical outcomes, adverse experiences, and so on for the patient.

DR. PACKER: That means that the committee knew if there was bleeding?

DR. SAX: The committee was just provided the adverse experience pages. So if there were bleeding episodes, they would have known that too.

DR. PACKER: But that means that the committee did know if there was bleeding?

DR. SAX: Yes.

DR. PACKER: Jeff.

DR. BORER: I would like to follow up with that same idea a little bit. I looked through the books we were sent. They say, in general, that therapy that was given after a conclusion of the test drug infusion was generally evenly distributed among the various groups. But nowhere in the presentation that I saw, although I may have missed it, was there any mention of other antithrombotic or specifically platelet-active drugs that may have been given other than aspirin which was the background for everything. Can you tell us a little bit about the use of other antithrombotic agents after the cessation of the test drug infusions? Were they actually evenly split among the various groups?

DR. SAX: I can tell you very little about the antithrombotic therapy after the first 24 hours after study drug cessation. In other words, for the first 24 hours after study drug cessation we continued to collect concomitant therapy in great detail.

I can tell you that the use of open-label heparin during that 24-hour period occurred in about 50 percent of patients and was equal between the two study groups. Other

agents such as nonsteroidals were generally prohibited by the protocol or discouraged by the protocol until the completion of therapy, this being our first study. And the use of the nonsteroidals were also evenly distributed. But the main one being heparin, again, the switch from a study drug to open-label heparin occurred in about half of the patients. Some of that was in the setting of angiography. In fact, a lot of it was in the setting of angiography. In fact, a lot of it was in the setting of angiography because angiography tended to occur in the first 24 to 48 hours afterwards. And a little over -- about 60 percent of the patients had angiograms so a lot the heparin use was in that setting. That is the main antithrombotic. After that we do not know.

DR. BORER: That seems reasonable enough for PRISM because the prespecified endpoint was measured at 48 hours and the other subsequent analyses were sort of adjunctive, although I would sort of like to know what happened to drugs through the 30-day assessment period, although you are not up to that point yet. I would flag the fact that I would like to know about this with regard to PRISM-PLUS and RESTORE too where the prespecified time of assessment was later and, in fact, the time of greatest interest is later still. So, if you do not have that stuff, maybe somebody could start looking it up so that when you get to it we will

have it.

DR. PACKER: Marv?

DR. KONSTAM: Rick, I have two questions. The first -- maybe you answered this in response to Dan or Milton. But just so I am clear, was the endpoint -- could the endpoint committee identify endpoints either with regard to unstable angina or MI that were not investigator initiated?

DR. SAX: The endpoint committee had the discretion to do that, but it occurred very infrequently.

DR. KONSTAM: How might that happen? Were there enzymes, for example, that they had access to?

DR. SAX: Yes. They had access to enzymes. What happened, again, throughout the trials and in particular the setting of procedures after a PTCA, there may be an enzyme elevation that the committee reviewed that the investigator did not identify as an MI and the committee then would adjudicate that as an MI. That pretty much was -- it would be that sort of situation. But, again, that was quite infrequent for the two unstable angina trials.

DR. PACKER: But how did they do that? I mean, how did they get access to a database that -- other than the ones that were generated by the investigator reporting mechanism. I guess that what we are all asking is that we really do need to understand the process by which this

occurred. Again, let me emphasize again why we are asking this. Of the three components of the primary endpoint, this is the most subjective. And of all the three components of this primary endpoint this is what drives the treatment effect. And, therefore, one needs to be -- I guess that the committee really wants to know as much as it can possibly know to understand how this endpoint was defined, how the adjudication process worked, and how patients who were not reported by investigators were included as events. Did Merck screen the database for enzymes and send it to the adjudication committee even though the adjudication committee had not received an investigator report?

DR. SAX: Let me address Dr. Konstam's question directly and then I will address yours again. May I have slide 529?

Just to show you how infrequent the committee-identified endpoints were, the one additional case of refractory ischemia here, a few additional ones with heparin. These additional cases of refractory ischemia were likely to be cases that were identified perhaps as the investigator as an infarction, but then they may have been switched to refractory ischemia. There is one additional infarction in each group, and one additional unstable angina.

To answer your question, Dr. Packer, yes, the

database was screened as part of the routine data cleanup process. And so elevated enzymes, as part of the database screening were looked at. If we identified elevated enzymes above the upper limits of normal, we went back to the investigator and asked the investigator to reconsider the case and the investigator then, if they felt it was a new infarction, would submit a revised case report form. Or if they felt it was not, but we felt very strongly, we might ask the committee to further adjudicate that particular case. But the committee did have access to all of the enzymes on the patients that were identified and were sent on to the committee.

DR. PACKER: But, again, please remember that -- can you put the slide back up? If these are the additional endpoints that the committee added to those submitted by the investigator, I guess -- is that correct?

DR. SAX: That is correct.

DR. PACKER: I guess I am struck by the fact that for the area that we think is the most subjective, which is refractory ischemia, the committee added six in the heparin group and one in the Tirofiban group.

DR. SAX: But, again, this is a very low number relative to --

DR. KONSTAM: Rick?

DR. SAX: Yes?

DR. KONSTAM: Do you have an analysis that looks at these endpoints based on investigator judgment as opposed to endpoint data?

DR. SAX: Yes. I will ask for Dr. Snapinn to discuss that.

DR. RODEN: While that slide is coming up, I just need a little clarification. At the end of the trial, the sponsor went through the database and looked at the enzymes and flagged enzymes that might have reached an endpoint that had been ignored by other investigators. Is that what we just saw or is that a separate --

DR. SAX: No, no. What you just saw were the endpoints that were identified by the endpoint committee that were not identified by the investigators, where the endpoint committee may have switched an endpoint or the endpoint committee may have --

DR. RODEN: So, how often -- do you have a table that tells us how often at the end of the trial once the database was being reviewed and elevated enzymes were being identified how often were those events reclassified?

DR. SAX: I cannot tell you that, Dr. Roden. That was an iterative process that was part of the routine data cleanup during the course of the study. So, if we saw a patient with elevated enzymes, we would note that. As part of checking for adverse experiences and so on, we would send

a message back to the investigator saying that we identified elevated enzymes. Did you miss something here? And the investigator could respond yes or no and change the case report form appropriately.

DR. RODEN: I understand the difficulties in getting all of this perfect. I am just trying to -- maybe I can ask it another way. Do you have a number that tells us how often the investigator-declared endpoint that he or she sent on to the events committee was left intact by the events committees? In other words, how many of the events that drive this process were actually pristine events as opposed to reviewed or re-reviewed, or re-identified events?

DR. SNAPINN: Yes. I have a slide to look at that point. Before I talk about this I have one quick comment on the previous numbers that you saw. Those additional --

DR. PACKER: Could you speak up just a little bit. We have transcribing responsibilities.

DR. SNAPINN: The numbers that you saw previously on additional endpoints brought up by the endpoint committee, not suggested by the investigators were for the entire 30-day duration of the trial, not necessarily primary endpoints for 48 hours.

Okay. Now I would like to show --

DR. PACKER: How many were 48 hours?

DR. SNAPINN: I do not know what proportion of

those were within 48 hours. Clearly, the readmission for unstable angina was not.

Okay. This slide shows the overall results based on the endpoint committee, adjudicated endpoints versus the results proposed by the investigator initially. What you can see here is that the endpoint committee rejected roughly equal numbers of endpoints in each of the two treatment groups which is very consistent with what I would expect and hope that an endpoint committee would accomplish, that is, removing some of the noise and leaving more of the section (sic) intact.

DR. PACKER: Maybe I can try to ask the question in a different way. I understand that there are a very small number of events added to the database by the endpoint committee. It is seven events in the area of refractory ischemia. But they do happen to split 6-heparin, 1-Tirofiban. I guess that this slide sensitizes us to the fact that, depending on how we look at this, the P-value might change. I understand that we are all hovering around a P value of .05. If you were to look at this -- I guess what I am concerned about is that the process was not -- normally, this process is thought to be fairly straight-forward. The investigator identified an endpoint and, in his or her best judgment, sends it in as an endpoint. The adjudication committee -- and the only reason it exists is

to reduce noise -- basically says yes or no and then it goes forward. Here there was an additional process that went on with an attempt to identify a few additional events.

DR. SAX: May I? I am sorry.

DR. PACKER: Sure.

DR. SAX: I think that the process is almost as simple as you have described it. The endpoint committee, as you can see, there were very few events that were identified by the endpoint committee. That is, to some extent, a process of reviewing the case and perhaps switching from an MI to refractory ischemia, refractory ischemia to an MI. The process, as you have described it, of investigator-identified endpoints being adjudicated yea or nay by the committee is essentially what happened here.

DR. TEMPLE: I think what everybody wants to know is exactly how the extra events that arose would have been given to the events committee so that they might consider it. Because it was unbalanced, six to one. It is obvious what is going to happen if you take those out. It is going to not look as good. How exactly did those additional events get to the committee for adjudication?

DR. SAX: The case report forms, as they were identified by the investigators, were submitted to the committee. There were no additional events generated during the process. The committee --

DR. TEMPLE: Somehow the committee found six events.

DR. SAX: Again, that may have been a switch of events, something -- a switch of events from one to another.

DR. TEMPLE: No. That is not what it is. It is 6-1-1-1 and it is not --

DR. SAX: No, I understand that. But what I am saying is that there may have been -- the committee may have taken, for example, may have taken a patient who was identified as a readmission, and it turned out that there may have been a mistake on the case report form. The patient was still in the hospital. Things like that occurred during the course, but there were no additional events. The events that were submitted to the committee were investigator-identified events that were adjudicated. The committee -- if there was a case that was controversial or the investigator, it was unclear, a case like that may have been submitted to the committee as well. But, generally, these events had to be identified by the investigator.

DR. TEMPLE: So, if the investigator did not identify an event as a possible event, it never got to the committee, could not get to the committee, no way; is that right?

DR. SAX: There may have been a few events where,

for example -- and these would occur largely with CPKs, not with refractory ischemia -- where we, as the sponsor, may have asked the committee to review an event, but I do not recall particularly when that might have occurred.

DR. TEMPLE: I think that that is what Milton is asking about. How would that have occurred? Who? You know, would those people have been absolutely, unequivocally blinded, right, Milton? Is that your question?

DR. SAX: Yes. Well, if that occurred, it would have been with my looking at a case and saying that there is something controversial here, there is something that needs clarification, and something added on to the committee. But we were completely blinded to that process. That process was conducted in a completely blinded way here, manner.

DR. RODEN: I guess a typical scenario might be that you would find a set of enzymes that you think might have hit an endpoint.

DR. PACKER: We cannot hear you.

DR. RODEN: I guess that the difficulty would be that if you find a set of enzymes that you think might have constituted an endpoint a year later and go back to the investigator and say think about this again, they have to make a judgment as to whether there was checking during that time or unstable T-wave changes during that time. That can be a difficult judgment.

DR. SAX: Yes. The number of new infarctions identified by the committee was one in each group. So largely these cases might be a case where the investigator may have said there was an infarction but the endpoint committee felt there was not enough evidence for infarction but there might have been evidence for refractory ischemia or something like that where a case may have been submitted as an infarction but switched. But there was nothing in the process where, as part of the process, new events that were not investigator-driven could easily be generated. It is not part of the process.

DR. PACKER: JoAnn.

DR. LINDENFELD: Just let me be sure I understood the slide. Over a third of the events that the investigators judge to be events were not judged to be events by the CEC? Is that a correct reading of that slide?

DR. SAX: I am sorry.

DR. LINDENFELD: In other words, the CEC said that the investigators in the Tirofiban group said there were 6.8 percent events and that was downgraded to 3.8 by the CEC.

DR. SAX: Yes.

DR. LINDENFELD: Isn't that an unusually large number to be changed?

DR. SAX: No, I --

DR. SNAPINN: I am not sure if it is an unusually

large number, but it is comforting to see that it was equal numbers in the two treatment groups.

DR. LINDENFELD: Well, but it changes the significance of the result. I mean, it seems like over a third -- for the CEC to judge a third of the investigator-defined events, more than a third were not events just seems like a large number.

DR. SAX: Again, this was a fairly rigorous process requiring objective evidence of ischemia. By and large, the rejection of events for refractory ischemia was because the event committee was not comfortable that ischemia had been adequately documented.

DR. LINDENFELD: It points out the difficulty in this endpoint -- [comment off microphone] -- events.

DR. PACKER: Can you speak up, JoAnn? We are having microphone difficulties.

DR. LINDENFELD: This just points up where -- were most of those events that were not considered events refractory ischemia? They must have been.

DR. SAX: I think that Dr. White may want to comment about this also. Dr. White was the chairman of the steering committee for the PRISM study.

DR. PACKER: We cannot hear you.

DR. WHITE: I am Dr. White. I am privileged to speak. We were concerned about the low event rate in the

trial and, therefore, we encouraged very strongly for the investigators to over-report, if possible. We wanted a high event rate to have power for the trial. I am comforted to see that the investigators actually did that and that when the adverse events committee reviewed the events, they lowered the numbers based on pre-specified, strict criteria for the endpoints. So I am actually comforted about that. We did work very hard to get more events reported.

DR. PACKER: I hate to say it, but I guess I do not understand that. If you want more events then you do not have an adjudication process to eliminate events.

DR. WHITE: No, I do not think you understand what I said. The adverse events committee has a very important role to adjudicate events. The issue is under-reporting. you are always concerned that not enough events go to that committee. That committee has strict criteria and that is very important. They are concerned that an investigator does not report an event that could be, for example, refractory ischemia in this situation. And so we wanted all of those to be reported. We wanted any concerns, any doubts, we wanted to raise those events so that they could be adjudicated in a blinded way. I am sorry if I have not quite --

DR. PACKER: No. I understand that the criteria that were in place here were not strict. They were not

strict criteria. These were guidelines based on the judgment of the endpoint committee. This is a process that is not easy to adjudicate.

DR. WHITE: Let me just -- and Rick could back me up -- these were strict to the extent that you had to have ECG findings specified, one millimeter ST depression or T-wave inversion. You had to have episodes of pain within one hour, either 20 minutes, or two 10-minute episodes. So those were strictly defined through optimal medical therapy. And I think that those three criteria are very important. So we said to investigators that we want to see all of these events. We want them to be adjudicated. As I understand the process, the adjudication committee found that some of the cases did not fulfill those criteria, the ECGs, or whatever. Do you want to add to that? I mean, it was strictly pre-specified in terms of time, ECG, and optimal medical therapy. Although the latter one did require more judgement than the other two.

DR. PACKER: We will go Bob Temple, Lem Moye, Marv Konstam, and Dan Roden.

DR. TEMPLE: It is my understanding that the Duke group has just reported an analysis of investigator versus adjudication committee results on a number of trials. I do not know if Rob can talk about that or not. But they tend to go a variety of ways. Sometimes there are more events,

sometimes there are fewer. Sometimes it favors the drug, and sometimes it does not. That should hardly surprise anybody since it is actually encouraging that it goes multiple directions.

One of the reasons that we usually tell people that this is not the best endpoint are all of the reasons that you are giving here. Of course, our alternative choice is urgent intervention. People could say that that is just as subjective as whether you have refractory angina. My question, however, is did you -- what happens to people whose angina is refractory at 48 hours? Do they just sort of sit there until a heart attack happens or do they go to a procedure? If they go to procedures, did you also do an analysis of need for urgent intervention, which is an endpoint that we have asked a lot of people to look at?

DR. SAX: If I could address the overall impact of refractory ischemia and then we could look at that. I can address it even better for the PRISM-PLUS study which I will come to. Let me give you an idea of the overall impact of refractory ischemia. Not only is this meaningful to the patient because there is a very high likelihood of going on to procedures or having other cardiac events. But it is even more meaningful long-term to the patient.

If I could have slide 675 please?

These are the data from the PRISM study. They are

also the day from the PRISM-PLUS study. But if you had refractory ischemia within 48 hours, you will see that over the first 30 days your likelihood of having either an MI or death was increased over five-fold over the cohort as a whole, and your likelihood of dying was a five-fold increase as well. That was equally true if you had refractory ischemia even in the off-drug period up to seven days -- nearly seven-fold increases of MI and death, still almost a five-fold increase of death. Just for comparison, if you had an MI, obviously, you would have a high likelihood of dying or having another MI. But an MI within seven days carried almost a very similar prognostic value to refractory ischemia. So this is an endpoint that I think is identifiable and does carry with it prognostic significance.

I think that it might be more appropriate to talk about the use of procedures in the context of PRISM-PLUS. But, in general, if you had refractory ischemia, there was a very high rate of angiography and, then, of course, what happened after that depended upon the anatomy found on the angiogram as to whether a patient did not get revascularized, but there was also a high rate of revascularization.

DR. PACKER: But, Rick, I think that you would admit that these calculations would have been just as powerful that you just showed if you had just done the

investigator-initiated events only.

DR. SAX: I think that the investigators -- we have not done that analysis. We have done the analysis on the basis of the committee review. Because, as Dr. White indicated, we asked the investigators to submit cases that they thought met the definition but also submit cases that they wanted to be reviewed. But since the events moved in the same direction, I think that the analysis would be comparable. It may be not as powerful because it is not as precise. The committee did remove noise.

DR. PACKER: Lem.

DR. MOYE: Yes. I am wondering if you could help me to understand the choice of an endpoint on the primary analysis which commences after a period of two days. In clinical trials we always have to live with the limitation that if you follow people long enough everybody is going to have bad events eventually and event rate curves come together. This is true even if you follow people for years. here you follow people for a matter of days. We find a significant differences, which was a protocol-specified, primary endpoint analysis. There is no question about that at two days. But, at seven days we do not see anything. I am just struggling with how to integrate that into the fund of knowledge.

I mean, does the medication have no efficacy, have

no benefit conferred after a week, but, in fact, it does work for two days? How do you explain that?

DR. SAX: Let me try to put that into some context. The PRISM trial had an objective which was to look at the drug effect. It was designed really to be a pure test of drug effect. We expected the drug to, as a hypothesis, that is the way we structured the trial to reduce cardiac ischemic events for medical stabilization only. We wanted to look at the drug at the end of the drug effect so that the drug follows standard, if I could say, pharmacodynamic principles and the principle of trial design that you look to see where your drug effect is.

Once you shut off the drug there would not be any intrinsic reason to expect that the drug effect would linger unless other things might be going on. That is why the PRISM trial was designed in this way. We knew by the trial design that we were not going to be able to use concomitant heparin, we would not use concomitant procedures. And we know that in the management of patients that these things would be used.

We wanted this to be a test of the hypothesis that an antiplatelet agent alone could be used to affect and change the medical management of this syndrome.

To address your question, however, we designed PRISM-PLUS. PRISM-PLUS was really to address what happens

in the management of patients. How do you use the drug optimally to get long-term effects? That trial was designed to address the question that you are raising.

DR. MOYE: Just one more question. What happened with death at 30 days?

DR. SAX: Ah, death at 30 days. In the PRISM trials, deaths were significantly reduced at least by a nominal P value from three -- I believe the numbers are 3.6 percent to 2.3 percent. And the P value for that was .02. So there was a significant reduction in deaths at 30 days. We could come back and discuss that if you want.

DR. MOYE: Even though you had I think two more deaths; is that right?

DR. SAX: At 48 hours there were two more deaths. There were six deaths in the Tirofiban group versus four. By seven days, the trend towards reduction of mortality was apparent and the curves did separate at 30 days.

DR. PACKER: Marv?

DR. KONSTAM: Could you speak a little bit to the maintenance of the blinded nature at the sites in the setting of -- and this is applicable here and also to the PRISM-PLUS trial where you have groups randomized to heparin or not to heparin. Can you speak a little bit about how you manage that and still maintain everyone at the site blind?

DR. SAX: Yes. Because of the nature of the fact

that Tirofiban has no effect on the APTT, but heparin, of course, needs to be titrated to the APTT, and the APTT, the protocol recommended titrating the APTT to two times control, we have to go through a rather elaborate system to keep the blind in the study. That was done by a double-dummy infusion. So that every patient received two bags. One in the PRISM study -- just to keep things simple because it was a Tirofiban versus heparin comparison -- every patient received two bags. One bag for patients randomized to Tirofiban contained active Tirofiban, and the other contained nothing. It contained a placebo, just an infusion. Patients randomized to heparin, that bag would contain heparin and the other bag would contain a placebo. So there was a double-dummy infusion.

The blinding, and we went through very elaborate procedures to protect the blind at every site. This was just part of the trial set up, where blood samples were sent down to the laboratory identified as study patients, and the laboratory was to remove the analysis of those samples from being reported back in anyway to the patient chart. Every site had an unblinded investigator in this study who received those trial results and those APTT results for titration were kept separately from the patient's chart ad infinitum. They have been kept separate.

Now, the investigator, of course, knew the

randomization code. If the patient was on heparin they were given a nomogram to adjust the heparin. If the patient was on Tirofiban they were given dummy instructions for the titration of Tirofiban. And so what was communicated from the unblinded investigator back to the staff taking care of the patient was just an adjustment increase by two CCs per hour, decrease by two CCs per hour, give boluses. There was a vial that contained placebo where they were to draw up boluses of heparin to maintain the blind. So it was a fairly elaborate process.

DR. KONSTAM: What was done to prevent the local sites from drawing their own APTTs in the middle of the night?

DR. SAX: It could be done. It did happen inadvertently in a very small number of cases where there was a break in the blind, but it was in the realm of maybe one percent of cases where we were notified of the blind being broken in that sort of way, some inadvertent APTT. But, in general, we instructed the sites to put a sign on the patient that the Tirofiban study, or the MK3 study, APTTs were handled in a special way. We gave the sites special labels for the vials and so on. The labs were briefed. This was all set up as part of the in-servicing of the site. So there was special labeling, special notification.

Every site had a documented set of procedures that were signed off on by all of the people involved. The laboratory had the unblinded investigators with site-specific standard operating procedures to handle the blinds.

DR. THADANI: Rick, I had a couple of issues. I am surprised that you said that you did not expect the drug effect to last beyond 48 hours. When you are doing trials such as this, you would think the beneficial effect would persist. I realize the pathophysiology. Once you stabilize the plaque, would you look at the heparin/aspirin data, continuation of aspirin preserve the effects of initial benefit at least in pilot studies, not large trials? So is that a retrospective conclusion really when you design the trial or you felt that we were only going to be seeing it at 48 hours and there would be nothing else?

DR. SAX: No, no, quite to the contrary. We prospective -- and the trial as you see it is exactly what we prospectively identified. We focused on, again, people with pharmacodynamic principles so that we would look at the drug effect. We realized that after we shut off the drug that there would be other things that would go on, switch-overs to open-label heparin, and especially procedures. We wanted this particular trial to be unconfounded by procedures. Once you start doing procedures, you know that there are additional complications of procedures, additional

infarctions, and so on. This trial had a very specific goal. Look at the role of an anti-platelet agent. you have to realize that the standard of care was aspirin and heparin, and we wanted to test the hypothesis tat an anti-platelet agent alone could have an effect on medical management. That is all that the trial was designed to do. That is why we set the 48-hour endpoint.

Again, PRISM-PLUS, as you will see, had a different set of objectives to really look at the overall management. This trial had a very specific goal.

DR. THADANI: Another issue regarding that. In the inclusion criteria, patients could have coronary heart disease and could have chest pain without ST changes as inclusion criteria.

DR. SAX: Yes, this trial --

DR. THADANI: And yet, in your outcome measures, you are mandating ECG changes plus chest pain. What happens to a patient who had a one-hour chest pain. The cardiologist thinks that he is got unresponsive to therapy, and he goes to the -- [comment off microphone] -- would that be counted as refractory or not? Because he did not have ST changes he is not counted as refractory. How many patients were there in that database?

DR. SAX: I cannot answer that question specifically about how many patients were counted as

refractory but may have as ECG changes. Again, the endpoint committee was fairly strict. They wanted to see good, objective evidence that the patient was ischemic and was failing medical management. And the endpoint committees were fairly rigorous about that. I could not tell you --

DR. THADANI: I sympathize. Those are the difficulties you see when you are managing these patients because your criteria for inclusion does not include SC changes. The patient might have gone because the enzymes are elevated. And then he got chest pain and you rush him to the cath lab and it will not be captured. It could happen in both groups. I am not denying that.

DR. SAX: Yes.

DR. THADANI: Those are the difficulties with soft endpoints.

DR. PACKER: JoAnn.

DR. LINDENFELD: Just so that I understand. If a patient had refractory ischemia within the first 48 hours judged by the investigator, then they could have gone to angiography and had a revascularization.

DR. SAX: Yes.

DR. LINDENFELD: But they might not have been counted as refractory ischemia by the CEC.

DR. SAX: The committee would have reviewed all of the evidence. So that the committee would have reviewed the

angiograms and the investigator's decision. But, as it turned out, there were times where the investigator did, in fact, classify the patient as refractory, did take them to the catheterization and perform a procedure, and the endpoint committee rejected that. That is indeed the case, as they felt that the investigator may have taken the patient to the cath lab without the patient being truly refractory.

DR. LINDENFELD: And that could have been -- that was probably a fairly large number of events.

DR. SAX: It did not happen very often, but it did occur.

DR. LINDENFELD: The difference was 6.8 versus 3.8 percent in the first 48 hours?

DR. SAX: 5.6 percent versus 3.8 percent.

DR. LINDENFELD: That was the CEC event. So there was a difference of three percent absolute?

DR. SAX: Yes.

DR. PACKER: Can we pursue that? That means that if an investigator submitted a patient with unstable, with refractory ischemia the endpoint committee said no, the patient went on to have angioplasty and PTCA within 48 hours and, during PTCA suffered an MI, did that count?

DR. SAX: Yes, as an MI after the 48 hours.

DR. PACKER: No. Within 48 hours.

DR. SAX: I am sorry. I was just listening to the cases as you defined it.

DR. PACKER: Let me specify it because it is a critical point. You have a patient who goes in -- you try to preserve the integrity of the endpoint by saying that no one should have a procedure until they had an endpoint, but then 40 percent of the endpoints were adjudicated out of the process. The -- if a patient had an MI, went for a procedure so that the investigator thought that they had refractory ischemia, they had an MI during the procedure within 48 hours --

DR. SAX: That would have counted as a myocardial infarction.

DR. PACKER: That would have counted as an MI and with the endpoint -- well, how would the endpoint committee have known that they got all of the events in the first 48 hours, they got the events that the investigator submitted during that the investigator believed constituted an endpoint?

DR. SAX: The endpoint committee had the complete case report form so that the investigator -- the scenario that you have outlined indeed could have taken place. I do not know that it did, but it could have taken place, where an investigator felt that the patient was failing medical management on a Friday afternoon and could have taken the

patient to the catheterization laboratory. In the catheterization laboratory within 48 hours, they had a complication of an angioplasty and the patient had an infarction. That would have counted as an endpoint. The investigator may have classified that as refractory ischemia. The endpoint committee may have said, no, this represents not refractory ischemia, rejected that, and classified that as an infarction.

DR. PACKER: Even if it occurred after a procedure?

DR. SAX: Even if it had occurred after a procedure.

DR. PACKER: Okay. That leads to the next question which is the medical reviewer identified that in the PRISM study somewhere between 11 and 12 percent of patients failed to complete the study.

DR. SAX: Yes.

DR. PACKER: That is 12 percent in the Tirofiban group and 11 percent in the heparin group. And they stopped either because they -- the major categories were that someone thought that they had an endpoint and other categories, primary category was adverse reactions and, I guess that another category are administrative reasons or globally distributed as administrative reasons. When a patient's stopped, was discontinued from the study within

the 48-hour period were events that occurred after they stopped, after they had discontinued but within the 48-hour period counted?

DR. SAX: Yes. This was conducted as intention to treat and all events were counted. It had nothing to do with whether the patient had discontinued or not.

DR. PACKER: Remember that intention to treat just says that you analyze according to randomized signs.

DR. SAX: Yes.

DR. PACKER: It does not say that you analyze for the intended duration of therapy.

DR. SAX: No, but we -- no, but we analyzed all events that were -- all events were counted.

DR. PACKER: For the intended duration of therapy. How many patients were actually -- did not provide complete data for the 48-hour follow-up? How many patients --

DR. SAX: We had no loss to follow-up.

DR. PACKER: No. Okay.

One last question. I guess you have heard the committee express concerns about the adjudication process. I guess realizing that there was a significant difference between in the incidence of drug-related adverse reactions in this study, nearly twice as many patients experienced drug-related adverse reactions in the Tirofiban group than in the heparin group. Why did the adjudication committee

have knowledge of the adverse reactions?

DR. SAX: Again, we submitted the whole case report form to them for review.

DR. PACKER: Okay. Ileana.

DR. PINA: Just one follow-up on Dr. Borer's question, Rick. We have a very elaborate analysis here of concomitant therapy at the time of presentation. Do you have any data on what additional therapy the groups received and was it evenly distributed? Because most physicians when they see someone having recurrent ischemia are going to do other things beside anti-platelet agents.

DR. SAX: Yes. We actually looked at all concomitant therapy and concomitant therapy was evenly distributed. But, in particular, we looked at anti-anginal therapy, the nitrates, beta-blockers, and calcium channel blockers and those were evenly distributed between the two treatment groups, concomitant therapy.

DR. PACKER: Okay. Can we proceed with a presentation of PRISM-PLUS?

DR. SNAPINN: Excuse me, Mr. Chairman. I would like to get back to a question which came up earlier in the discussion. The committee was somewhat concerned about the additional seven refractory ischemias that were identified by the endpoint committee. We have gone back and taken a look at the statistical analysis, assuming first of all that

all six of the additional cases in the heparin group were within 48 hours which we do not know, and removing them, leaving in the one case in the Tirofiban group, we still get statistical significance. So the result did not depend on those additional cases. The P value is .041.

DR. PACKER: .041?

DR. SNAPINN: Yes.

DR. PACKER: Okay. Can we proceed with PRISM-PLUS?

Agenda Item: PRISM-PLUS

DR. SAX: Sure. Okay. Let me turn to PRISM-PLUS. This is the trial of therapy in the setting of both medical management, medical stabilization, and interventional therapy for non-stable angina, non-Q-wave infarction. It is this trial that forms the basis for our indication.

Like PRISM, this trial contained a 48-hour period of medical stabilization during which procedures were not to be performed unless the patient reached a clinical endpoint. Unlike PRISM, however, again, here we continued to study the drug through angiography and through angioplasty if angioplasty was clinically indicated. Thus the drug could be continued through this second period of thrombogenic risk.

Now, the primary hypothesis for this trial was compared with heparin, either Tirofiban alone or Tirofiban

with heparin will reduce the composite endpoint of refractory ischemic conditions, new myocardial infarction, and death of any cause at seven days in patients with unstable angina, non-Q-wave infarction. The trial thus had two pre-specified treatment comparisons, the Tirofiban plus heparin comparison versus heparin, and Tirofiban alone versus heparin.

I would also add that there was an angiographic substudy as part of this trial to look at the effect of therapy on thrombus burden to attempt to link the potential benefit of treatment with the effect on the underlying pathophysiologic basis of the disease.

Shown here is the study design for the PRISM-PLUS trial. Again, there is a 48-hour medical stabilization period, but then the drug was allowed to be continued for up to 108 hours through angiography and through angioplasty if an angioplasty was performed within this window and could be performed so that the study drug could be continued for at least 12 to 24 hours after the procedure. We were interested in the medical stabilization period, so we had a secondary endpoint at 48 hours. But because we were looking at the overall treatment regimen and the overall strategy, we specified our primary endpoint at the end of seven days. We were also interested in longer-term follow-up, so we had a secondary endpoint at 30 days, and there was pre-specified

follow-up in this trial to six months.

At 30 days, at seven days, actually at 30 days and 180 days, we also counted readmissions for unstable angina. And like in the PRISM trial, here too, the endpoints were investigator-identified and were adjudicated by an independent endpoint committee blinded to the treatment group.

This trial too was conducted under the auspices of an independent data safety monitoring board. As I mentioned, there were two treatment comparisons, Tirofiban alone versus heparin, and Tirofiban plus heparin versus heparin. And to adjust for these two treatment comparisons, an interim efficacy analysis, the critical P value for this trial was set at 0.025.

There was one sample size readjustment during the trial. The original plan sample size of 420 patients per group was increased to 735 patients per group here according to a protocol-specified rule.

It was at the time of this interim efficacy analysis that the Data Safety Monitoring Committee recommended to the Steering Committee that the Tirofiban alone arm for this trial be dropped.

This has been extensively discussed in your background package, but I will briefly summarize. The concern of the Safety Committee at the time they reviewed

the data which was just after approximately 300 patients had been enrolled in each group was that there was an apparent excess of mortality. This excess mortality was related primarily to cardiac ischemic events. This represented 14 deaths in the Tirofiban alone arm versus four deaths in the heparin arm. There was an excess mortality at the seven-day time point.

As it turned out, this excess mortality was not significant at 30 days or at six months. The findings of this trial, as Dr. Moye has pointed out, are inconsistent with the PRISM trial where there was actually a mortality benefit for Tirofiban alone.

Because the trial was designed upfront to have two separate treatment group comparisons with an appropriate conservative adjustment of the P value to declare statistical significance, the arm being dropped does not alter the analysis of the Tirofiban plus heparin versus heparin comparison. So all subsequent analyses I will be discussing will just present the Tirofiban plus heparin versus the heparin comparisons.

So, let me show you the results of the PRISM-PLUS trial. Shown here is the time to event curve for the primary composite endpoint at seven days, from the time of randomization to seven days. At seven days there is a reduction of the primary composite endpoint of refractory

ischemic conditions, new myocardial infarction, and death from 17.9 percent in the heparin control group, to 12.9 percent in the group receiving Tirofiban plus heparin.

This 17.9 percent reduction -- 17.9 percent event rate to 12.9 percent event rate in the Tirofiban plus heparin group represents an odds reduction of 34 percent and was highly statistically significant with a P value of 0.004.

Again, looking at the components of the composite, refractory ischemia was reduced from 12.7 percent to 9.3 percent, and myocardial infarction from seven percent to 3.9 percent. This represents a 47 percent odds reduction and in and of itself was highly statistically significant. At this time point deaths were infrequent and were equal between the two treatment groups.

To further understand the overall benefit of Tirofiban on refractory ischemia/myocardial infarction, we looked at the effect of the therapy during the initial phase of medical management. These are the time to event curves for the first 48 hours and, again, after the 24 hour period, there is a separation of the curves so that the heparin group had an event rate of 7.8 percent, and this was reduced to 5.7 percent in the patients receiving Tirofiban plus heparin. Again, remember, this is before the patients underwent procedures.

Although I have not shown this on this figure, at this time point, at the 48-hour time point, myocardial infarctions have already been reduced with an odds reduction of nearly 70 percent and a P value at that time point of 0.014. Thus, there appears to be medical benefit in the study for Tirofiban plus heparin, again, before procedures take place.

So, turning now from the short-term effects to the longer-term benefits, this Kaplan-Meier curve shows the event rates up to 180 days. On this figure, the reductions are displayed in terms of risk reductions for the comparison of heparin versus Tirofiban plus heparin. The early benefit of reduction of cardiac ischemic events at seven days is maintained for the 30-day period with a risk reduction of 22 percent and an absolute difference of 3.8 percent. The P value for this was 0.039. The benefit was also maintained out to six months. At six months the event rate was reduced from 32.1 percent to 27.7 percent, an absolute difference of 4.4 percent, risk reduction of 19 percent, and a P value of 0.024.

Not only was the composite endpoint positive, but shown here is the Kaplan-Meier curve where myocardial infarction and death, which represents irreversible cardiac morbidity. As I have discussed, this was significant at seven days with a P value of 0.007. The benefit was

maintained at 30 days with an absolute reduction of 3.2 percent, a risk reduction of 30 percent, and was maintained at six months, again, an absolute reduction of three percent, a risk reduction of 22 percent and in and of itself approached statistical significance.

Deaths throughout this period remain comparable between the groups at all time points. So the findings are consistent with the drug regimen that effectively reduces early myocardial infarctions and then preserves this benefit for at least six months.

We also looked at the trial for consistency of effects at the primary endpoint. This is various subgroup analyses plotted on a log scale for odds ratio, again, at the primary endpoint. Again, you will see that there is good, consistent effects across the pre-specified subgroups of age, gender, clinical presentation, unstable angina, non-Q-wave MI. The diabetics, in particular, had a very good effect in the study, antecedent heparin, antecedent aspirin, and, of course, the various countries that were involved in this study.

Now, let me turn to the angiographic sub-study which provides further objective mechanism-based support for the clinical results. Angiograms were to be performed between 48 and 96 hours or earlier if clinically indicated. It is important to note that since the angiographic films

are before interventions, the outcomes are representative of the benefit of medical therapy only.

All available angiograms performed between hour zero and 97 were sent to a core laboratory for blinded analysis. The evaluable angiograms were graded by the presence and severity of thrombus based on the TIMI classification. TIMI blood flow past the culprit lesion was also assessed.

Shown here is the analysis of thrombus grade based on possible, small, moderate, large, or recent total occlusion. There was an overall reduction in thrombus burden with an odds ratio of 0.77 and a P value of 0.022. In particular, for the patients who had clear evidence of angiographic thrombus, that representing thrombus grades moderate, large, or recent total occlusion, the event rate for thrombus in the heparin group of 24.1 percent was reduced to 17.1 percent in the patients receiving combination therapy with Tirofiban plus heparin.

In addition, when TIMI flow past the culprit lesion was assessed, the percent of patients with limited TIMI flow, namely TIMI zero flow, representing a total occlusion, minimal perfusion with TIMI-I flow, or partial perfusion was reduced from 25.5 percent in the heparin group to 18.1 percent in the Tirofiban plus heparin group. This represents an odds reduction of 35 percent and was

statistically significant with a P value of 0.002.

The angiographic sub-study, therefore, demonstrates that Tirofiban plus heparin reduces thrombus burden and improves blood flow past the culprit lesion. These findings present clear mechanistic support for the reduction of clinical events seen with combination therapy. This occurs again before revascularization procedures take place.

So let me briefly summarize the results of PRISM-PLUS that I have presented so far. Tirofiban effectively reduces cardiac ischemic events, including the composite of myocardial infarction and death. This benefit can be seen as early as after 48 hours of medical stabilization before procedures, through angiography and angioplasty. And the early benefit is sustained to six months.

Furthermore, the angiographic study links the pharmacologic effects of combination therapy on thrombus which is the pathophysiologic basis of the disease with the overall clinical benefit seen for the treatment of unstable angina, non-Q-wave MI.

Now, I would like to make one other point about the PRISM-PLUS study. This has to do with outcomes based on whether the patients underwent revascularization procedures.

This figure shows the percent of patients who underwent cardiac procedures during the trial. In this

study angiography was expected by protocol, not mandated, but expected. In fact, almost 90 percent of patients underwent angiography during the initial hospitalization. It turned out that about a third of the population underwent angioplasty. About a quarter of the population underwent coronary artery bypass surgery, and the remainder of the patients, nearly half of the population, were medically managed.

To further examine the consistency of the drug effect across the population, in keeping with our proposed indication, I would now like to review with you a new analysis that has been requested of us by the FDA. This analysis reviews the outcomes based on whether the patients underwent angiography, bypass surgery, or had medical management and were not revascularized. Please recognize, however, that at the time of the clinical presentation, at the time of admission it is not known what the ultimate treatment therapy will be. And so this analysis is -- the cohorts for this analysis are based on events that occur in this time period and the decisions that occur here. These cohorts are, therefore, post-randomization cohorts. This analysis, therefore, should be interpreted with caution.

Shown here are the 30-day outcomes for the overall patient population, again, plotted on a log scale representing odds ratios. This is the overall patient

population. Shown here are the patients undergoing angioplasty, bypass surgery, and the patients who ultimately had just medical management. Again, these odds ratios represent all events from the time of randomization through 30 days irrespective of whether the events occurred before or after a procedure.

Notice that the treatment effect of Tirofiban plus heparin was not limited to any one cohort and, in fact, overall, each of the cohorts had a treatment effect that was generally comparable with the overall patient population. This was true both for the composite endpoint of 30 days and for the endpoint of myocardial infarction and death. In particular, the patients who had or just underwent medical management alone had endpoints of 30 days that were comparable with the overall benefit seen for revascularized patients as well.

To further refine this analysis, we did look at events prior to revascularizations which also represents a period of medical stabilization. As you can see, there was a benefit for Tirofiban plus heparin even before an angioplasty and even before patients underwent bypass surgery.

Now, the outcomes of patients who undergo angioplasty are of some interest because, as I have discussed, this represents a period of time where GP

IIb/IIIa agent could exert an additional benefit. So we looked specifically at the events from the time of angioplasty forward, recognizing again that this is a post-randomization cohort.

This figure is a time-to-event curve taken from the time of procedure, from the time of angioplasty. There was a prompt separation that occurs with an absolute reduction of the composite endpoint of 6.5 percent at 30 days representing a 46 percent risk reduction at this time point. And this benefit seen at 30 days was maintained to six months with an absolute reduction of 5.6 percent and a risk reduction of 25 percent.

These findings are suggestive but, again, by no means definitive of an additional benefit for Tirofiban in the subset of patients undergoing angioplasty even beyond the benefit seen during the pretreatment period as part of the overall management strategy of these patients.

Now, a third study directly examined the benefits of Tirofiban.

Agenda Item: Questions and Answers

DR. PACKER: Can we pause? I think that we have some questions on PRISM-PLUS. We will begin with our primary reviewer, Dan and Glen.

DR. RODEN: Thank you. We do need to have a discussion of why it is that Tirofiban did so well against

heparin in PRISM and did so poorly against heparin in PRISM-PLUS. I will just leave that out there for a while.

I have two comments to start off with. One is with respect to the angiograms. The agency, in their summary, provided the data not just for the Tirofiban plus heparin in the heparin arms, but also the Tirofiban alone arm. I guess that it is a small point, but the patency rates, the TIMI-III flow rates are as high with Tirofiban as with the combination. So that really does not support the argument that there is a link directly between the pathophysiology or the proposed mechanism of this compound and outcome since this was the group that had the worse outcome and yet angiographically had just as good an outcome as the best group. That is one comment.

What I really want to add --

DR. SAX: Dr. Roden, could I just clarify one thing?

DR. RODEN: Sure.

DR. SAX: If I could have slide 368? If you look at the overall thrombus grade, this is the Tirofiban low norm. You will see that the rates of absent thrombus -- I am not going to go through the various classifications -- but you will see that, if you look at Tirofiban alone as compared with heparin with respect to thrombus grade, the presence or absence of thrombus and the individual

components look very similar. In fact, as you look at the overall outcomes in this study, recognizing that there is only -- these are contemporaneously enrolled cohorts, remember that at the end of the study there were over 600 angiograms in this group and over 600 angiograms here. So this is the contemporaneously-enrolled cohort. The findings here do support the ultimate outcomes which in this cohort suggested that the composite event rate of 30 days was very similar between Tirofiban and --

DR. RODEN: I was referring to the flow data and not to the thrombus data.

DR. SAX: Again, the number of angiograms here is not that great. But the thrombus --

DR. RODEN: 243. It is a small point because it does not actually impact one way or the other on efficacy. But, if you want to make a big deal out of how Tirofiban improves flow compared to heparin, then you really need to include the Tirofiban data. That was not my major question.

I wanted to come back to this issue of patients who have to undergo procedures in their outcome versus patients who do not undergo procedures in their outcomes. The data that the agency provides, and I hope that the numbers jive with yours, are that -- talking about the primary, the pre-specified primary endpoint, the seven-day endpoint, there were 100 patients in the Tirofiban plus

heparin group who had an endpoint and 143 in the heparin alone group. So that is a benefit of 43 patients, a delta of 43 patients.

I flip to another table that the agency has provided to me and these are patients who met the composite endpoint at seven days and who had a procedure. Now the Tirofiban plus heparin number is 95 and the heparin alone number is 135. That is a difference of 40 patients.

So the way that I would read that is that the benefit of this compound is limited virtually exclusively to that group of patients who undergo a procedure. In the complementary group of patients, which is smaller that did not undergo a procedure, the numbers -- I do not have the numbers, but the math has to turn out that there will not be a difference between the two because the difference between the two groups is absolutely preserved when you make those two comparisons.

Have I made that completely unclear or just a little bit unclear?

DR. SAX: I follow your argument. But I would like to point out just a couple of things. First of all, if you look at the numbers as opposed to looking at what happened in the trial, I could see your point. However, if you look at what happened in the trial, at 48 hours, we already saw a benefit for Tirofiban plus heparin and that is

before procedures.

If you look at the analysis requested of us at the FDA and look at the patients who underwent procedures even before they had procedures, there is a benefit for Tirofiban. If you look at the medically-managed patients who never got procedures, recognizing, again, that those patients are a subgroup that excludes everybody who had procedures and look out to 30 days, those patients had a benefit. So, in terms of what happened to the patients as opposed to the absolute numbers calculated at seven days, you are seeing benefits in all of those groups of patients.

DR. MOYE: I have just a question that concerns me about the methodology that maybe you can put to rest very quickly. For this examination of post randomization cohorts, was the analysis you showed us time-dependent?

DR. SNAPINN: If you are referring to the survival curves that we showed, those show the events that occur subsequent to the time of the procedure. So time zero on those curves is the time of the procedure, and we are counting events that occurred subsequent.

DR. MOYE: Okay. There is a little difficulty there because you have undone the randomization, haven't you?

DR. SNAPINN: Correct. That is why we are concerned about interpreting those with caution.

DR. MOYE: So am I.

Also, in generating P values, looking at the effect of therapy in those cohorts, how did you -- did you divide the trial population into cohorts and then examine within each cohort what the effective therapy was which I think is not the best way to do it? Did you use a time-dependent covariate analysis?

DR. SNAPINN: Well, one point is that we have not calculated P values on any of these analyses involving non-randomized subsets for the reasons that we just discussed. But we do present, of course, odds ratios and confidence intervals. For those analyses, the initial slide that you saw showed all events just breaking the population into cohorts without time-dependent covariates, just three separate cohorts.

The second analysis you saw, the second slide then split up the events that occurred, for example, in the PTCA cohort into events that occurred prior to the PTCA in that cohort and events that occurred subsequent to the PTCA in that cohort.

DR. MOYE: I guess my own experience with this is that you can get a very distorted picture of the effect of therapy within post-RC cohorts unless you do the time-dependent covariate analysis. I would just like to -- yes?

DR. LIPICKY: It is not their fault, Lem. We

asked them for that.

DR. MOYE: I was not pointing a finger, Ray.

DR. LIPICKY: Well, no, I understand, but they are the ones who seem to be getting blamed. The notion of that analysis was that if you accept the fact that the primary endpoint was met and you are now going to say this trial found something, can you do anything that will allow you to develop insights into what this effect was that it found other than if you randomize people and give them drug and there is a net benefit of some kind? And, indeed, there were no P values or anything else. It is a very kind of intuitive thing. It probably was not a good thing to ask for. But you do get some insight. Dan got some good arguments out of it.

DR. MOYE: One other quick point. I do not believe that treating PTCA as a time-dependent covariate gets you out of the same confounding bind. I believe that the analysis is just as confounding.

DR. LIPICKY: It is not a randomized population.

DR. MOYE: That is right.

DR. LIPICKY: So you cannot unconfound that.

DR. MOYE: One other question. I wondered if somebody could clarify for me what the exact protocol specification was for the DSMB to decide to almost double the sample size for this experiment? My primary concern was

was this to be based on an examination of control group event rates or on an examination of efficacy?

DR. SNAPINN: Right. Could I have slide 620 please? The answer is that it was based entirely on the control group event rate. We recognize that re-estimating sample size based on a treatment group difference would not be valid. So to ensure that the DSMB could not make any use whatsoever of the treatment group effect, there was a pre-specified rule for them to follow which you see on this slide. They had no option to make a decision on their own. They simply had to follow this pre-specified rule.

At the time of the interim analysis, the heparin group event rate turned out to be slightly above 15 percent. They followed this rule. The rule told them to increase sample size to 2,205, which works out to 735 per treatment group.

DR. PACKER: Lem, before going on, let me ask the -- this was a trial originally designed with three arms. The sponsor appropriately took the two possible comparisons, each versus placebo. I assume that the comparison of Tirofiban versus Tirofiban plus heparin was of sufficiently secondary interest and that no alpha was spent on it and, therefore, worked with a P value of .025 as the critical P value.

Once a decision is made to drop the arm, does one

recapture the alpha or is the alpha in that arm spent and that all subsequent analyses that are made at the end of this trial are to be made at a .025 level?

DR. MOYE: The safest thing for the investigators to do is to continue on as they had planned, unless they had a prospective plan to recapture the alpha. I think that recapturing alpha is really a hazardous undertaking. There really are not very clear guidelines about it and it is very murky going.

DR. PACKER: Now, to make things even murkier, all of the P values that we have seen therefore need to be compared with either .025 or conversely, which might be easier for us to do, need to be multiplied by two; is that correct?

DR. MOYE: I would just compare them to 025.

DR. PACKER: Right. So that, Dr. Sax, when you refer to what your P values that you are showing for all of the supportive analyses are nominal P values?

DR. MOYE: Yes, that is correct.

DR. PACKER: And we would mentally have to think of this threshold as being .025? Bob?

DR. TEMPLE: Well, I do not think that that is self-evident. People could debate this interminably, and that would be a lot of fun, but we would not get finished. The correction certainly must apply to the primary endpoint,

and that is why they used .025 as the critical value.

I think that a lot of people would disagree about what you have to do with the MI component of that and all of that stuff. But, you know, you have got to keep in mind that there was another group for a while. It is at least somewhat debateable whether having met your primary endpoint you have to keep adjusting everything all of the time for every subgroup and every subset and all of those.

DR. HUNG: This is Jim Hung, FDA's statistical reviewer. I would like to make a comment and respond to Dr. Packer's question. If you have two armed studies, two arms compared with placebo and then in the interim you decide to drop a two arm based on the medical efficacy or something or reasons, then if you remove the remaining alpha to the other arm, then that total error would be inflated. But if you do not remove, if you do not reallocate that un-used alpha for the remaining arm, then that is okay. It is on the conservative side.

DR. PACKER: Without belaboring this point, because I think that all of the points that have been taken and made have been well-taken, if a protocol said that if one of the arms were dropped that the alpha would be recaptured, does that fix the problem?

DR. HUNG: No, I do not think so.

DR. MOYE: I suppose, if you said that you were

going to make a determination and you were going to spend say 005, 0.005 on determining whether to drop an arm or not, and you said that prospectively, then that allows -- you have approximately 0495 left for the other comparisons that are going to be -- that remain to be prospectively identified. But I think to decide on the fly that at an interim point if you have spent, if you discontinue an arm and therefore are not going to do any analysis in the end, can you recapture alpha, well, you have already done analysis at this point. How much have you spent at this point? I mean, sometimes we are counting angels on the head of a pin and we probably do not need to go into it in very much detail here now. But it really is very tricky.

DR. PACKER: I guess we should not lose site of the fact that on the stated primary pre-specified endpoint that the P value is significant even at the .025 level. So this is a perhaps more theoretical discussion. The only reason I asked was to more interpret the secondary analyses. And then Bob Temple's comment needs to be developed. It gets more complicated then.

DR. LIPICKY: Just to follow up on the P values. You did a pretty good job in PRISM of making .014 go to .076 for the primary endpoint. Can you do the same thing here?

[Laughter.]

DR. LIPICKY: Can you? I think that that would be

nice to see.

DR. PACKER: Let me see if I can translate what Ray is saying.

PARTICIPANT: Ray really needs translation.

DR. PACKER: This endpoint includes refractory ischemia. Was the adjudication process in this trial similar to PRISM? If it was, what happened? Tell us how it was conducted. Basically, we need to probably ask the same questions as we did for PRISM in PRISM-PLUS about the adjudication process. How many events were thrown out by the endpoint committee? What was the distribution? How many were added by the endpoint committee when the overall data in the trial was screened?

Believe it or not, all of that is encompassed by what Ray asked.

[Laughter.]

DR. SNAPINN: Can I have slide 609 please? This slide will show, again, the primary results as adjudicated by the endpoint committee side-by-side with the raw results submitted by the investigators. As you can see, the rate at which the endpoint committee rejected endpoints was smaller in this study than in PRISM, but that the result is still statistically significant at least to the .05 level.

DR. PACKER: No, it is not. No, no, no, no. The P value here is .025. We just went through that. So this

actually --

DR. LIPICKY: But his statement is correct that it is significant at the .05 level. It is just that you are demanding more than that.

DR. MOYE: Well, they demanded more than that. We are not demanding it. The investigator is demanding that.

DR. SNAPINN: And, in fact, we would hesitate to -- actually, I misspoke. I should not really be assigning statistical significance to a non-protocol-specified analysis. That is the endpoint committee analysis.

Another slide. If we could have 610 please? This breaks down the investigator-defined endpoints into its components. Now, unfortunately, I do not have these side-by-side with the endpoint committee results by components, but you can refer back to your packages to compare them. But what you can see here is that we still have excellent results within components based on investigator-defined endpoints.

DR. TEMPLE: How do you do that? Every one of them is less than the composite. Every one of them is a component of the composite. The P values are more extreme. Somehow the composite endpoint comes out less?

DR. SNAPINN: Yes. We noticed that also. It struck us as unusual, but it is true and it relates to how they over -- how the events overlap in the individual

patients in the different treatment groups.

DR. PACKER: I guess I am a little bit confused.

DR. TEMPLE: As Jeffrey points out, they do not have death up there alone.

DR. SAX: There was a hundred percent agreement on deaths.

DR. SNAPINN: Right. It is not there because of the agreement.

PARTICIPANT: That is good.

DR. PACKER: Maybe I can ask the question in a different way. I guess if this committee could go through in a reiterative process the concerns that it expressed in PRISM about the softness of refractory ischemia, the adjudication process that relates to it, and, I guess to -- and one thing which we have in PRISM-PLUS which we did not have in PRISM is an analysis of death in MI. I guess we all feel that there is -- that is an important analysis to look at. One, it tends to be far less subjective. Secondly, it is a process which represents irreversible harm. It is also an endpoint which has been used in other antiplatelet trials as a primary endpoints which allows us to think about this in a more holistic fashion.

Since there was total agreement on deaths, how much disagreement was there on MIs?

DR. SAX: We can show you the data that we showed

you on slide 610 and we could compare it back and forth. These are the investigator rates for myocardial infarction, 5.7 percent in the Tirofiban plus heparin group versus the heparin group, and the rates for MI at the primary endpoint.

DR. PACKER: Yes. I think that the risk reduction as adjudicated is 30 percent with a P value of .0 -- I am sorry. I am actually comparing seven days. If you look at the seven-day, the investigator-adjudicated events are I guess all across-the-board less frequent even for MI.

DR. SAX: The committee events just for comparison. These were investigator-identified MIs, 5.7 percent here and at the same time .7 days. The comparable number was 3.9 percent. For heparin it was 8.8 percent. And the comparable number was 7.0 percent for the endpoint committee. So the reductions, again, the committee was removing the same number of events in both treatment groups about 1.8 percent. Again, the committee was applying, as you would expect, a much more rigorous review.

DR. PACKER: Which is why, I guess, in all cases, the P values for the adjudicated analyses are smaller than for the investigator analyses.

Udho?

DR. THADANI: I have a couple of points. One of the issues -- I am not sure, just for my clarification. Originally the protocol was designed to look at a 48-hour

endpoint, and then he changed it before, trial completion to seven days.

DR. SAX: No, the protocol --

DR. THADANI: In the initial protocol it said 48 hours with a primary endpoint. But then, as the trial started it was changed to seven days.

DR. SAX: Yes. The very, very first protocol that was sent out to the investigators looked at a 48-hour time point. While that protocol was being sent out for IRB approval, the steering committee met and said, no, this is an overall treatment strategy, and you really need to look at the seven-day time point because you are continuing the drug beyond seven days. So, you are absolutely technically correct, but there were really no patients randomized at the time that that switch was made.

DR. THADANI: And point two, I think which is more relevant here, we saw the PRISM study really showing early benefit not at seven days, 10 days with the drug alone. In this one we are using a strategy where the patient comes in, you give him the drug, but 90 percent have to have angiograms. And the event rate could be lower in the group. But even post-hoc analysis is possible. Angioplasty will somewhat modify the event rate. So we have to add that to a new dictum, say that the drug is to be used, everybody should have an angiogram and this algorithm because that is

how to preserve the benefit at 30 days and 180 days. Had you not done that, then the catch-up phenomenon might have neutralized it. I would like your comments on that.

DR. SAX: Yes, again, the protocol did not mandate angiograms, but it encouraged angiography.

DR. THADANI: 90 percent. I think it was driven by angiograms, the study.

DR. SAX: 90 percent of patients did have angiograms. I think that the key answer to your question though is that before these angiograms were performed, we were already seeing benefit with an odds reduction of infarction of nearly 70 percent. Even if you consider the fact, and this is the analysis that the FDA had requested us to do, that even if you considered the fact that patients did go to bypass surgery or they went to angioplasty, the group that was leftover and had just medical therapy still had benefit from the drug.

DR. PACKER: Okay. Let's see, nearly everyone on the committee wants to ask a question. Tom, JoAnn, John, and Ileana.

DR. GRABOYS: I want to touch on the treatment selections. It is interesting that 90 percent -- actually get into the what is called maximal medical therapy, and who defined the decisions as far as maximal medical therapy, what it is and decisions to go on to angiography or any

further intervention. It is not surprising that 90 percent went on to the cath. But what is a little surprising to me is that only 47 percent remained on medical therapy. In the community, if you are cathed, you get about a 99 percent chance of going ahead and being intervened on with either cabbage or angioplasty. So the 47 percent figure to me is a little bit of a surprise. I am curious about what criteria were used either to continue on medical therapy or to intervene or was that simply at the discretion of the individual practitioner?

DR. SAX: This was entirely at the discretion of the individual practitioners. The protocol did not mandate therapy one way or the other based on the findings of the angiograms. I would just add that the findings are very consistent with what has been seen in multiple clinical trials, namely, a half to two-thirds of the population of unstable angina patients will go on to angiography in global trials. That may be somewhat higher in the United States. Then, based on the findings of the angiogram, patients will be triaged, if I could use that word, to ongoing medical therapy, bypass surgery, or angioplasty. And the split, the breakdown after angiograms falls into approximately one-third distributions, a little bit more towards maybe angioplasty currently. The numbers that we are seeing here are consistent with what is --

DR. GRABOYS: No. I understand that that is consistent with the trials. It is not necessarily consistent with what is going on in the community though.

DR. LINDENFELD: I would be interested in knowing the percentage of patients in PRISM and PRISM-PLUS who were revascularized within the first 48 hours, if there was a difference in the groups in those two studies. I am just trying to get back at this difference between what investigators identified as events and the CEC did.

DR. SAX: Just give me a moment, and I will find that for you. Okay. Could I have slide 338? Okay. These are the data from PRISM-PLUS of the revascularizations within the first 48 hours. You can see, again, we -- by protocol restricted revas procedures, unless the patient had a clinical endpoint.

There was already a difference in the treatment groups between the patients who were receiving heparin and the patients receiving Tirofiban plus heparin. Most of these procedures were angiography. About half of those patients went on, actually, a little bit less than half went on to some form of revascularization. Most of that was angioplasty.

DR. LINDENFELD: That actually makes me feel better about that difference that we have seen.

My other question is what was the mean duration of

infusion in PRISM-PLUS?

DR. SAX: The mean duration across the study was 71.3 hours. So, on average, the patients got three days of study drug.

DR. LINDENFELD: The reason I ask that is just that being that the results are most impressive in that study and this is a relatively short-acting drug, it is of interest that the longer infusion may be of more benefit.

DR. PACKER: It was also an infusion through procedure.

DR. LINDENFELD: Right.

DR. PACKER: John.

DR. DiMARCO: You have not said much about the Tirofiban arm alone. I am just curious about it. Am I correct in my interpretation of the tables that most of the deaths occurred between 48 hours and seven days, the excess deaths, in that arm of the study that led to the dropping of that arm?

DR. SAX: Yes, that is correct. In fact, most of them occurred between three days and seven days.

DR. DiMARCO: Were they in people who had undergone procedures? We might say doing a procedure on Tirofiban only then is not a good idea without heparin?

DR. SAX: In fact, most of the deaths occurred after study drug had been completed. I think that there

were only two deaths or three deaths that occurred during the study drug period. So most of the deaths occurred after the study drug had been stopped, but before seven days. The deaths almost uniformly were due to cardiac ischemic reasons, progression of the disease, if I could put it that way. Some of them occurred in the setting of procedures. some of them did not. I think that the split was about as even as to those who did have procedures or those who did not have procedures. But there were some deaths after bypass surgery and some deaths that occurred after angioplasty, yes.

When we look closely at these deaths, as you might anticipate, we could not find a clear relationship of the deaths being related to procedures. It is a confounded analysis. Because, in fact, they may have been rushed to procedures because they were more ischemic.

DR. PACKER: John, while we are on this topic, I guess I thought that it was curious in the way that both the sponsor and the medical reviewer described the mortality results in PRISM and PRISM-PLUS that they described the mortality results in the original trial of PRISM as being worrisome because they went in the wrong direction, leading to DSMB -- I am sorry, in PRISM-PLUS they went in the wrong direction because -- enough to cause the DSMB to stop an arm. And then the analysis of mortality at 30 days in PRISM

went in the opposite direction and that was deemed to be reassuring.

I guess I was not either reassured or alarmed by either. These are extremely small numbers. We know nothing about what this drug does to mortality. It is quite likely that the directional changes in both PRISM and PRISM-PLUS are due to the play of chance.

DR. SAX: If I can just comment. I think when one looks at the data exactly as you have stated, the numbers are small. If one looks at this we can say a couple of things. The deaths were not due to the drug toxicity. They were not due to bleeding. They were not due to thrombocytopenia. They were due to progression of underlying cardiac ischemia. And exactly as you have indicated, the number of deaths in the PRISM-PLUS arm where Tirofiban was dropped was very small and represented a 30-days, 21 deaths, versus 14 deaths. In PRISM the findings went exactly the opposite direction. If one were to perform a pooled analysis of this, it looks like there was a very slight benefit for mortality, even if one tries to match the cohorts for risk, a slight benefit for mortality for Tirofiban of 0.3 percent. But, overall, I think that one could say that in the respective trials, the mortality directions is probably due to the play of chance.

DR. PACKER: Ileana.

DR. PINA: I have two questions. On the patients who did not undergo any angiography, and I understand, Rick, that the numbers are small, the duration of study drug was much shorter than in the other groups. Was that specified in the protocol that if the patients were not going to be angiogrammed there was a shorter duration of infusion?

DR. SAX: We did not specify the duration of the infusion. What we did request was that if the patient was to undergo angioplasty that the infusion was to be continued for 12 to 24 hours after angioplasty.

So for the patients undergoing angioplasty, the overall duration of infusion was a bit longer than the other cohort. After angiographies, physicians had a choice as to whether they wanted to stop the drug immediately after angiography. That was done in about two-thirds of patients, or continue on. For example, if the patient wanted to go to bypass surgery, they had the option of continuing drug further.

If you continued -- after angiography, if you did not stop drug at the time of angiography, on average, drug was continued somewhere between 15 to 19 hours after angiography. But actually about two-thirds had drug stopped after angiography.

DR. PINA: Do you have any data on how long the patients were off of infusion before going to bypass?

Because that would have clinical relevance in telling people when they needed to stop this before sending the patients to bypass. The time on drug between PTCA and bypass are almost identical.

DR. SAX: We do not have specific data on the duration of therapy before bypass. But we do know there were very few patients who actually went to bypass surgery within 12 hours of stopping study drug.

DR. PINA: So they went later than that you are saying?

DR. SAX: By and large, patients were off study drug for more than 12 hours. We actually recommended that study drug be stopped before 12 hours. But the drug is short-acting. So, if you stop the drug say four to six hours before bypass surgery, most of the drug effect would be gone by that point.

DR. PINA: One last question if I may. It seems that a lot of the difference that we have seen here statistically relies on the myocardial infarction rate. Do you have any data on the CPK levels in both of the groups? In other words, does the drug not only perhaps prevent myocardial infarction? In the patients who have it does it modify infarction? Since I am looking ahead that a lot of the mortality that we see later on in groups is related to myocardial infarction and how much ventricle is left, do you

have any data on ejection fractions post infarct?

DR. SAX: We do not have any data on the ejection fractions. Remember the angiograms were performed generally early on. We have not looked specifically at ejection fractions in those.

With regard to CPKs, we do not have specific data on the CPK elevations. In PRISM-PLUS the protocol required at least a two-fold elevation of CPKs above the upper limits of normal or a re-elevation after -- if one came in with a non-Q-wave MI. In the setting of angioplasty, we required a three-fold elevation. In the setting of bypass surgery, we required new Q waves.

I can tell you, although I cannot tell you the exact numbers of the CPK levels by fold, three-fold, five-fold, 10-fold, in PRISM-PLUS that distribution was about two-thirds non-Q-wave, about one-third Q-wave MIs.

DR. PACKER: Just to close the loop on some issues related to PRISM that we raised in PRISM that need to be addressed for PRISM-PLUS. The number of events added to the adjudication process that were not originally submitted by investigators in PRISM-PLUS was how many?

DR. SAX: If I could have slide 333 please? Very few.

DR. PACKER: How many patients did not -- I assumed that you followed the same procedures which is that

patients were followed through the intended duration of therapy for all events whether or not they were taking their study medications or discontinued for any reason. Is that a correct statement?

DR. SAX: Yes.

DR. PACKER: How many patients were in fact lost to follow-up at the primary pre-specified time point of seven days?

DR. SAX: There were no patients lost to follow-up at the primary endpoint.

DR. PACKER: How many patients were lost to follow-up at the secondary analysis at 30 days?

DR. SAX: If I could have slide 323 please? 0.8 percent in each treatment group. And then at 180 days slightly more patients were lost to follow-up in the Tirofiban plus heparin group.

DR. PACKER: Okay. Lem, this has been an issue that you have raised in the past. Do you have any comment on this?

DR. MOYE: Without anything particularly pertinent because of the analysis time. The primary endpoint has an analysis time of seven days. At seven days you have no loss to follow-up. Any kind of adjustment that would be done for the other follow-ups would just really be academic?

DR. SAX: Right. Because we do not know what

alpha to assign to them.

I guess the last question is a philosophical one but is important to the committee, which the committee I think will probably discuss in more detail during the questions. I think that it will be important to find out the sponsors view on this. This committee has seen and I guess will continue to see trials of antiplatelet drugs in patients with unstable angina whose primary endpoint is defined in a different way than in PRISM-PLUS and defined at a different time than in PRISM-PLUS. For example, we have seen trials where the primary end point is death in MI at 30 days. In PRISM-PLUS, the primary end point is death, MI, and refractory ischemia at seven days. Can you outline the sponsor's thinking as to why they would not have chosen a more objective analysis at a more distant and potentially more clinically-relevant time point?

DR. SAX: We believed, based on the drug that we were studying, that this drug would affect thrombotic events close to the time of presentation where thrombosis needs to be stabilized and, again, the fibrinolytic process for clot needs to be allowed to takes its effect. We believe that the drug would work to prevent early events.

The trials were designed to demonstrate that. PRISM specifically as we have discussed was specifically designed to demonstrate that. But that is true of PRISM-

PLUS and it is also, as I will show you, true of RESTORE.

If you look -- I would like not to speculate or offer guidance. I know that there is a question related to that. But, if you look at where the drug is working in all of the trials here, as well as other trials that have come before the committee related to angioplasty or other events, what this particular class of agents is doing is exerting an antiplatelet effect preventing platelet aggregation and reducing early events.

What you are seeing with the shape of all of the curves which I am cognizant of what the committee has seen, is that early separation of events related to the acute effect and then maintenance of the effect to show consistency, to show that the drug is not hurting the patients down the line, but maintenance of curves that move essentially in parallel long-term. We were looking at the drug effect. We wanted to show the drug affected early events and that the drug had a consistent effect -- sustained benefit long-term. That is what we have demonstrated.

DR. PACKER: I appreciate that. I think that what you just said is very, very important. Most of the -- I think that there is a consistency across the -- data across all trials with all anti-platelet drugs that the effects appear to be, in part, time dependent. That is, the

majority of the separation, what really gives you the treatment effect is something which occurs early and one then follows at your own peril, sort of hoping that the effect sort of hangs on for as long as you can during the course of follow-up. We have already seen that drugs like this can have a pretty dramatic effect on refractory ischemias which drove the endpoint in PRISM. So, again, the question is really a philosophical one.

We need to be careful on the principle of fairness that obviously the earlier you go and the more you include recurrent ischemic events the more likely you are to put your bar that represents a win lower and more easier to achieve. And the harder the endpoints and the longer you go the bar becomes higher and harder to achieve. What I would like to know is does that bother you?

DR. SAX: I think that there are issues -- you are asking me to speculate -- but I think that there are issues related to trial design and then related to looking at the consistency of data and the sustained benefit. i think that one needs to look at drug effects where the drugs are working. I think that the issues that you are going to raise are going to become somewhat apparent as we discuss RESTORE. But one can certainly choose endpoints, even long-term endpoints that are designed in such a way to really reflect early ischemic events. But I think that in terms of

looking at a short-acting intravenous agent to effect an acute syndrome, it is appropriate to look at the time points of which the drug are active and then ensure consistency of effect long-term. That is the way that these trials were designed.

The trials were also designed in a way to have a protocol of medical stabilization to look at that, angiography to look at the components of the various phases of the treatment of unstable angina. So the whole program broke those apart. In some ways, the design of the trials was, therefore, designed to decrease heterogeneity but also to look at specific components of the drug effect and to really understand how the drug worked. There are other approaches to do this. But I think, again, one needs to look at the drug effect for the treatment of what one intends to use the drug for.

DR. LIPICKY: Just to stick with the same topic, I think I would like to ask Milton's question in a slight different way. So let's say there is a terrific drug effect early but it does not matter at 30 days, so you draw these nice curves that look like they are parallel. But what is the quantitation that I should in fact be reassured? That is they look parallel, they look like they are the same distance apart, the P values for those curves certainly are not impressive. How does one have reassurance that this

apparently large effect early has any meaning for any period of time at all?

I think these are different trials. And to look to be assured that the drug works in the way that you would expect from its biology and that maintains its benefit and has an appropriate safety profile.

DR. KING: I am Dr. Spencer King. I am from Emory University. I was the Chairman of the Steering Committee for the RESTORE Trial which we have not come to yet. But we spent a lot of time thinking about this initial effect and the long-term effect for all of these trials. And the thing that has been evident to us, of course, are the events that are defined continue to accumulate. As the years go by, we get more and more events. So the relative difference, of course, gets smaller, and smaller, and the P value goes away.

The real thing that I have been interested in is if we can prevent acute complications of whatever the events are early. Then we want to make sure that the absolute difference is sustained over time, indicating that there is no adverse accumulation of events. But the therapy that is being given is to effect the platelet-mediated thrombosis that is happening in the early phase. It is not affecting progression of coronary disease, re-narrowing after angioplasty, death from cancer, automobile accidents, or

whatever happens long-term. But we should see the relative difference in those events sustained over years. But we do not anticipate, if you measure the effect of an acute intervention at a far distant time point that you would -- that that would be an appropriate analysis.

DR. LIPICKY: It is sort of in the eye of the beholder, that is what should I do put a ruler down on those Kaplan-Meier curves and measure the distance between them and then if it looks like there is a millimeter difference I say, oops, that is not quite right? I must admit when I look at the curves I am not reassured. When I look at the quantitation that goes with the curves that does not reassure me anymore, although it is consistent with this difference being preserved. I am just looking for what you are offering that in fact the interpretation that it is is the correct one.

DR. KING: Well, the reduction in endpoints from this class of agents is probably related in part to their effect and in part to noise that may reflect other things that can happen to these patients. That difference must be, if there is a difference during the effect of the drugs then that probably reflects something that should be measured with appropriate power with the endpoint with the P value achieved. Then what I as a clinician would like to see is that the absolute difference that is achieved during that

timeframe does not change much over the followup indicating that no excess events are occurring in the other group. But I do not anticipate a widening of that effect or really a narrowing over time.

DR. LIPICKY: But how did you make that determination looking at the curves that were shown? How did you actually assure yourself? Did you do something? Did you measure something? Did you just look and say, oh, it looks okay? How did you actually convince yourself that the statement you are making is correct?

DR. KING: The only trial I was involved in was the RESTORE trial which we will come to. But I became assured of that in that the absolute difference in events during the early phase was identical to the absolute difference in events at six months as it was in some of the other trials of other drugs in this class, giving me reassurance that there was not excess -- that the early benefit of the drugs was not -- did not degenerate late because of some other events in the treatment group.

DR. PACKER: Jeff.

DR. BORER: I do not think that we ought to get too hung up on this issue of when did they look for the following reason. I do not think that there is any arbitrary time that we can determine that one should look at these data to know whether the effect is important or not.

In fact, what you want to do clinically is get to the next step, salvage the patient so that you can get to the definitive step, whatever that may be. Of course, that is always changing as new techniques develop. For that reason I liked what the sponsors did here. They looked at an overall patient management approach.

Now, having done that, we could cavil about whether seven days was the time to really do the analysis or 30 days was really the time to do the analysis. And that might be important were it not fir the fact that if you look at the data over time they are consistent, at least for PRISM-PLUS they are. Overall, it looks like people did better for seven days, certainly for 30 days maybe, for 180 days or whatever. So we may say that the data from all of the trials are not sufficiently consistent so that we can suggest that the drug should be approved. That is a separate issue and we have not come to that. But I am not sure that that it is appropriate for us to try and set a time point at which the analysis would have been appropriate. The real question is did we get them the next therapy because therapy is so complex. Did we manage the patient overall in the appropriate way? I think that that is the way we have to frame the question. That is sort of the way the sponsor has presented it to us from PRISM-PLUS at least. DR. PACKER: Jeff, my question one was

primarily a more philosophical overall issue in the development of all drugs in this therapy category for acute coronary syndromes. Of course, although I would agree with you that the internal consistency of the data in PRISM-PLUS is very reassuring, the selection of a time point for analysis happens to be a particularly critical one for the other two trials involved in this particular application.

I think that what we have heard from the sponsor not only today but also in the way that the protocols were designed is that they did actually believe that 30-day follow-up was important. It was a secondary analysis in PRISM-PLUS, primary analysis in restore. It has been used in other trials as a primary analysis. I think that there is a general consensus which I think that the sponsors also agrees with that objective events which are irreversible, are easier to interpret than events which -- endpoints which include recurrent ischemic events.

I am more concerned about the way that the deliberations of the committee provide perverse incentives to design our future trials. We have talked about that when we talked about Taso Sarton and the sampling of blood for liver function abnormalities. Again, the signal which emerges from this, not a treatment signal, but a design signal is that, unless -- you know, depending on how we deliberate, it would be sort of foolish for a sponsor right

now not to include recurrent ischemic events and to specify analysis that was as early as they could justify.

If I were in the audience right now doing a trial with a IIb/IIIa antagonist and I have death and MI at 30 days at my primary endpoint I would rush out right now, get an emergency meeting with the steering committee and change it. Would you agree with that?

DR. KONSTAM: I think that that would only be true if the drug worked. That is to say if the presumption is that the drug is working in the acute setting and, therefore, you are likely to see a significant effect early then what you are saying is right. But that is the presumption that the drug is doing what it set out to do. And then the flip side of that is if it does what it set out to do then I think that what you have heard a number of people say is that we would like to be reassured that it does not go back on that over the long-term. If the drug does not do what it is supposed to do acutely when it is being given, then it does not help to look at an early endpoint.

DR. PACKER: Yes, but, Marv, the Committee lives in a matter that it only sees the NDAs of the drugs that the sponsors think work. There is an enormous selection bias here.

DR. TEMPLE: There is more than one potential good

here. If every trial has to overcome the fact that the drug only works for 48 hours and has to show the effect hangs on and if you only count death and MIs, then every trial has to be pursuit size. It has to be 20,000. That means that you are going to have much less information on such other interesting question as dose response, interactions with heparin and all kinds of other things. So you pay a price for having to do trials, having to do mega-trials to get every answer.

If it is reasonable to think that the effect of an acute intervention is reasonably accessible at seven days or something like that, and that is not a crazy thing to do, it is not clearly a loss for society if you allow people to do that. It is not an inherent good to make every trial as large as possible. The question is whether that is reasonable.

Again, I guess you cannot talk about it, but there is an ongoing analysis of basically all of these trials. A hundred percent of them that involve short-term interventions showed that most of the effect occurs early and that after that, as you dwindle down to 30 days, there is not any catch-up, but you continue to accumulate events that are, for obvious reasons, not influenced by the 48-hour intervention. So it is not self-evident that the longest duration is the best. They are asking somewhat different

questions.

One possible approach to these analyses is to look relatively early and then ask a different question, a secondary question, if you like, about whether there is a worrisome tendency to catch up. Now, the power to answer that question is going to be very small. Maybe Ray's suggestion that you put a ruler on it is the best you can do. But it is not a crazy approach for a 48-hour intervention.

DR. LIPICKY: But I do think that Milt was asking that that judgement be made. That is that it could be because it is not self-evident that something that works for a few hours and has no impact 30 days later at all is in fact useful, and that the judgment needs to be made that you are comfortable in making judgements for 72 yours and not knowing very precisely what happens at 30 days.

DR. PACKER: No impact is not a correct description. You are talking about P values. You are not talking about impact. If you have a delta of 30 days at 48 hours and you have a persistent delta at 30 days, but you have now accumulated enough events so that the nominal significance disappears, that is not the same as saying no impact.

DR. LIPICKY: Well, but, no, I understand. But the problem is knowing that that is true. At the moment, no

one has given me a quantitative way of determining that.

DR. TEMPLE: No. That is a legitimate question. May I make a suggestion actually? I am writing a memo to you to propose this as we sit here. There is actually a lot of data on this point. There is in fact a meta-analysis on its way to the publisher. It might be reasonable for the committee to take a look at all of the available data on these acute interventions. There is quite a number of them now in place both IIb/IIIa inhibitors and others, and look that whole question over with data in-hand. Because there have got to be 12-13 studies now.

DR. PACKER: Dan, did you want to --

DR. RODEN: I guess one difficulty with looking at 30-day or 180-day endpoints which goes without saying but it needs to be said, is that the further you get from the controlled randomization situation the less control you have over all of those other things that happen to patients.

So, while I have some sympathy for Ray's view that who cares what happens at two days because we really want people to live longer -- in fact, for an acute intervention, the next step in the acute intervention is very institution and operator-dependent. And so looking at 30-day or 180-day outcomes, unless they are highly or tightly controlled may be pretty misleading.

I like Bob's idea of reviewing all of these

interventions of which we -- I mean, it seems to me at each one of the last three or four meetings we have had at least one intervention for unstable angina. I would like to have some sense of how to go about thinking about all of them together.

DR. PACKER: John, please go.

DR. DiMARCO: From my point of view, it is just a question of does the drug do what it says it is going to do which, in this case, is decreased ischemia in the first 48 hours or some short time period?

I think that the secondary question is how important is that in the long-term management of the patient? It does not really relate to what the drug does, but it may influence you whether you feel obligated to use this drug in a clinical situation.

DR. PACKER: These issues are quite complex. The committee actually is asked to consider this in a more philosophical sense in its series of questions both with respect to the inclusion of refractory ischemia as part of the endpoint. I think that also, of course, one can expand that to the issue of when one analyzes the data.

Let's put a book mark here and go on to RESTORE.

Agenda Item: RESTORE Trial

DR. SAX: In fact, the RESTORE trial will address some of these issues as well.

RESTORE was designed to study Tirofiban when initiated later in the treatment paradigm for unstable angina, namely after coronary anatomy had been defined and a decision had been made to treat the patient with an angioplasty. And then Tirofiban was initiated at the time of the procedure.

The primary hypothesis for RESTORE was that Tirofiban initiated at the time of a PTC or atherectomy will reduce the composite endpoint of repeat revascularization due to ischemia, stent placement used for abrupt closure, new myocardial infarction and the count of deaths of any cause compared to placebo and all patients received heparin and aspirin. The time of the primary endpoint was at 30 days, in keeping with the other trials in this field.

Note that, in this study, unlike other angioplasty trials that the committee has seen, we counted all revascularizations due to ischemia, not just those due to urgent procedures.

As shown here, drug was initiated in the catheterization laboratory at the time of angioplasty once a guide wire had been placed across the lesion that was to have the procedure. Therefore, unlike PRISM-PLUS, there was no pretreatment period in this study. Randomization of study drug initiated occurred after the stenosis had been crossed by the guide wire.

In this study because the drug was initiated in the catheterization laboratory, we used a bolus of 10 micrograms per kilogram infused over three minutes and then followed this with a maintenance infusion of 0.15 micrograms per kilogram per minute. Now, notice here that the higher infusion regimen was used because by protocol we have expected the investigators to stop heparin after the procedure and to remove sheaths and continue on Tirofiban alone in an attempt to decrease bleeding complications.

The study had two prespecified analyses at day two and at day seven. But, as I have mentioned, the primary endpoint of the study was at 30 days and we did follow patients long-term to six months.

As was the case with the other two studies, the study was conducted under the auspices of an independent data safety monitoring board. There were two planned interim efficacy analyses. As a result of this the critical P value for the trial was set at 0.047. The primary efficacy analysis of this trial was an all patients treated analysis. So that only patients who actually underwent the procedure and received study drug are included.

The trial had a somewhat broader population of patients with acute coronary ischemic syndromes than the other two trials and included not only patients who presented with unstable angina and non-Q-wave MI, but also

patients who presented with Q-wave infarctions. Patients had to have symptoms, but they could enter the trial within 72 hours of clinical presentation. These patients were also at high risk for clinical events based on the fact that they had to have documented electrocardiographic evidence of ischemia or elevated cardiac enzymes, or had to have thrombus present on the angiogram prior to being included in the study.

The slide just shows the baseline demographics for the RESTORE study. The population is very slightly younger, but a comparable age to the PRISM and PRISM-PLUS studies. About a little over of a quarter of the population was female, primarily Caucasian and, again, comparable histories of diabetes, hypertension, hypercholesterolemia.

You will see that about two-thirds of the population had unstable angina. About a third of the population as enrolled with infarction. This included seven percent of the population who underwent angioplasty for treatment of primary Q-wave infarction.

Now, let me show you the results of the RESTORE trial. Shown here is the time to event curve for the primary endpoint of restore which was at 30 days. As you can see at the time of the primary endpoint as specified, the trial was not statistically-significant. What you see is that the event rate in the placebo group went from 12.2

percent to 10.3 percent in patients with treated -- patients treated with Tirofiban. And, again, everyone received heparin and aspirin. This represents about a 17 percent odds reduction and, again, was not statistically significant.

The components of the composite endpoint, as I have described them however did trend in the proper direction.

Now, recognizing, again, that the primary endpoint of the trial was not statistically significant, we did look at the earlier event rates as it was specified in our data analysis plan, this being at two days and at seven days.

At two days there was a 40 percent odds reduction in clinical events. This benefit was maintained to seven days. This is consistent with a drug that has a potent effect of reducing thrombosis-related events early after revascularization, suggesting that the drug was preventing events related to thrombotic complications following the procedure. But after seven days, as you will see, the difference between the curves narrows somewhat. This, as it turned out, was due to an accrual of non-urgent revascularization procedures.

So to further look at the difference in endpoints in this trial compared with other trials in the field, we performed a post-hoc analysis of the composite endpoint

counting only medically-urgent revascularization events as part of the composite as opposed to all revascularization events due to ischemia as specified by the protocol.

These events were adjudicated in a blinded manner by the endpoint committee. This is the time to event curve for that analysis of the composite endpoint which includes only urgent revascularizations. What you can see is that the curves separate early. But after seven days the curves remain flat and virtually parallel.

This suggests that there is very little accrual of additional events after the first few days after the angioplasty.

Using this composite endpoint, the findings are consistent with what has been seen with other IIb/IIIa agents in the setting of angioplasty. I would be glad to discuss this further and the implications of the choice of endpoints at the end of the presentation.

So, now let me turn to the long-term prespecified follow-up for RESTORE at six months. Shown here are the six-month data for the restore trial for the composite endpoints again of all revascularizations, myocardial infarction and death. The absolute difference seen at seven days, 2.8 percent, was maintained at six months, although the trial was not statistically significant at the six-month time period. Again, this is consistent with the drug that

reduces very early events due to the effect on platelets and thrombosis with maintenance of this benefit to six months.

So let me briefly summarize RESTORE. The study design may not have allowed us to show an effect convincingly at the 30-day primary endpoint which included all revascularizations, there was clear evidence for the ability of the drug to reduce events early after the angioplasty. The findings are supportive, again, with the findings that were seen in the angioplasty population in PRISM-PLUS of the use of Tirofiban in patients who require angioplasty as part of their overall management strategy.

DR. PACKER: In our traditional way, we will pause and ask the committee if there are any questions about RESTORE. Dan, if you have any, Udho?

Agenda Item: Questions and Answers

DR. THADANI: I think that there are several issues which emerge from this trial. We heard that your drug is very effective. You block all of the platelets. And yet, in this trial, A, you elected -- rather than seven-day, you elected a 30-day endpoint for whatever reason, you know, showing the differences. And you were not able to show a difference. There is no statistical significance at 30 days. The data you showed was not significant. And yet we can always do statistics to show some different -- some time point. I am very sympathetic towards you that there is

some effect at seven days. As a clinician, if I am looking at ischemia or something I want to make sure that the patient at one month or even in post-MI trials would look at one month of mortality. If I am not benefiting him, am I doing something? So it is not -- I think it is the overall issue in all of the trials. What I am having difficulty here with is you are treating 2,600 patients, and you have really not shown a major benefit. Yet, in PRISM-PLUS, we saw a very clear-cut everywhere. Are the patient populations so different? Are we doing something wrong? Perhaps you could also argue that the reason you are not showing a difference, I am just suggesting that you did not treat the patient before-hand which may be very beneficial before you start interviewing the patients. I would like your comments on that.

DR. SAX: Yes. I am going to ask Dr. King to comment as well. I think that your hypothesis about pre-treatment is one potential hypothesis, but I would like to suggest another potential explanation which has not to do with the drug effect but the choice of clinical endpoints and the choice of trial design.

If I could just show slide 101 and then just very briefly show a couple of slides? This, again, was the primary analysis that, again, shows the narrowing of the curves between seven days and 15 days. But there are some

differences here, as I have mentioned, between what we chose -- and Dr. King will comment about this as well -- as our primary endpoint for 30 days and what has been done with other trials in this field.

Our trials, as with other trials, counted deaths due to any cause, non-fatal infarctions, and we also counted use of stents which has, of course, increased wince the early 1990s. But the difference here is whether one counts recurrent revascularization due to recurrent ischemia, in other words, revascularization for symptoms or just urgent or emergent angioplasties.

This is what happens if you just count the urgent angioplasties. You see this very rapid separation of the curves in this trial. And then, again, as I have mentioned, the curves remain flat. There was a very significant reduction in urgent angioplasties. But what you are doing is really counting just procedures which occur from the time of angioplasty for the next four to five days around the time of the angioplasty.

The same is true if you count infarctions. I know, Dr. Thadani, this has been an issue for you. In this study, we used a rule-out infarction protocol. We did not screen serially for CPKs. But whether you screen serially for CPKs, as has been done at other trials, or use a rule-out in my protocol as we did here, again, the events occur

very early with a slight accrual of events, and then stay virtually parallel. So, if you use urgent revascularization as an endpoint and you use CPK screening as an endpoint, what you are doing, even if you are counting events of 30 days is really just counting events that occur in this early period.

By the way, I just want to point out that the CPKs that we were picking up in this or worse, significant MI's, I think, Dr. Pina, you had a question about that for the other trials, but that is true for this trial.

Now, the interesting point about this is that if you look at non-urgent revascularizations that are occurring late between seven days and approximately 15 days, things go in the wrong direction, slightly in the wrong direction -- a high rate of non-urgent revascularization for Tirofiban versus placebo. But that effect is exactly what has been seen in the other IIb/IIIa trials. This is the EPIC Trial and the EPILOG Trials. And you will see if you look at non-urgent revascularizations both for angioplasty, there was a high rate of non-urgent revascularization, the 6MF plus bolus and infusion group, and a high non-urgent cabbage. And I do not have the data -- I have not seen the data for the 30 days for the EPILOG Trial. But you will also see the non-urgent revascularizations at six months also went in the wrong direction between either the SM Abbott fusions and the

placebo group.

So I think that what you are seeing is that these events are reducing -- these drugs are reducing urgent revascularizations, they are very potent at reducing infarctions that are occurring around the time of angioplasty. But I think, as Dr. Roden pointed out, the accrual of other events subsequent represents some noises. That is why we were not seeing events -- the statistical difference at 30 days the way that we specified the protocol.

DR. THADANI: So what you are really saying is urgent revascularization.

DR. SAX: Yes.

DR. THADANI: Because you have already done one vascularization.

DR. SAX: Right. Urgent repeat revascularization.

DR. THADANI: Repeat revascularization. I knew that that has to be emphasized.

DR. KING: I would just say that the Steering Committee must take some responsibility for the endpoint. You asked why we had this endpoint. There was a feeling of this Steering Committee that it should be clinically relevant as possible without much thought toward the drug action frankly. So, the 30-day endpoint was picked because that is a common endpoint for all kinds of things that just

seemed like a good number.

The revascularization for any ischemia seemed to be an event that we would say is an event that you would not like to have. So we did not specify for urgent which would drive events more related to this drug.

And the third thing is that we wanted to see clinically-relevant infarctions so we did not specify CK sampling at frequent intervals, only a CK driven by clinical events or a CK at the end of the 36-hour infusion.

So I must take some of the responsibility for the Steering Committee being more interested in the clinical endpoints some of which probably are not best tied to the effect of the drug.

DR. PACKER: But, Spencer, you have essentially I think hit the nail on the head and have crystallized beautifully in what you just said the dilemma that was outlined in the previous discussion period. Because, on the one hand, one would like to look at a clinically-relevant time, and on the other hand, one would like to look at a point in time when the drug is exerting its effect. One has no problem with those time points are identical. The dilemma that exists is when there is an either perception or a strong body of evidence to suggest that those two time points are not identical. I think that everyone here agrees with you. When you look at 30 days that seems like a

clinically-relevant time point. But, depending on how you define the primary endpoint and to what degree of catch-up you have from an early effect, you may or may not hit a P value at the clinically-relevant time point. So the motivation is to look not at the clinically-relevant time points but to look at the time point where you might see an effect. It is sort of like the old story about why someone who lost a watch over there is looking here because that is where the light is. That is a problem.

DR. KING: I think that the time point is interesting. I do not know what the clinically-relevant time point is. As I say, 30 days is sort of picked up from surgical literature and other things. That is one issue, the clinically-relevant time. The other issue, however, is the drug effect relevant endpoints.

In this study, I thin that it is contaminated with some non-drug relevant endpoint such as non-urgent revascularization. So when we try to make comparisons to understand drug effect, we are trying to understand the various different drugs, we have to appreciate the different adjudication procedures.

DR. THADANI: I think that before you leave you made an important point that CPK or MBs were not collected serially. It was driven by a clinical endpoint. The patient had chest pain. Now, we know if you did CPKs every

eight hours post-angioplasty, depending on when people change criterias, two times, three times, or whatever you want to define it, the infarct rate even silent is there. It may be eight percent, 10 percent. That could have driven your numbers totally different than what you are seeing here. I think that that is the problem with all of what we are seeing with the IIb/IIIa's, or heparin, or whatever. It is very difficult to come to grips if what one is seeing are different things. So, if you really want to look at the infarct post-intervention, I think that it is absolutely mandated that you at least should have three CPKs for 24 hours whether the patient has symptoms or not because, otherwise, the patients are going home 12 hours later. Some go home three days later. So I am not sure. You could argue that it should happen in both limbs. But, in the absence of data it becomes -- even the enzyme-determined MI becomes a softer endpoint as opposed to Q-wave MIs. So the question is what about Q-wave MIs? I realize that some patients had Q-wave MIs in the study. Those with non-Q-wave MIs, unstable angina, is there a difference in Q-wave MIs say at day seven or 30 days and forgetting about the enzymes which is not enough data in here.

DR. SAX: We do not have the breakdown of the Q-wave versus non-W-wave MIs.

DR. KING: Could I address that part about the CK

sampling? You are quite correct. I mean, if we look at 11 of the studies that have been done where sampling has been Q8 hours, the rate is eight to 10 percent of something. In this study it is about five percent.

The more endpoints there that are sampled, the greater the opportunity in this endpoint to see a difference. So this is another issue that is relevant to these kinds of studies that goes along with the time.

DR. THADANI: If your drug is effective, you should do more sampling. You should be able to show more of a difference because your hypothesis is going to prevent acute complications. So one would hope that it reduces the infarct -- you should look more often.

DR. KING: The clinical question present at the beginning of this trial which remains is the future prognostic value of the small CK risers which is still unclear.

DR. PACKER: Dr. Throckmorton, who is the FDA reviewer for Tirofiban.

DR. THROCKMORTON: I just had a small question. You showed your PRISM-PLUS data for the angiographic subset. I wondered if you wanted to comment on the longer-term protocol-specified substudy in RESTORE for the re-angiographics?

DR. SAX: Sure. I would be glad to do that.

There was a sub-study in RESTORE specifically to look at a question that was important at the time that the study was conducted as to whether the IIb/IIIa agents could affect restenosis. So we did an angiographic substudy in patients at specified centers where the centers agreed to perform a second catheterization at six months to look at the question of whether there was an impact on restenosis. The second films were sent to a core laboratory for quantitative angiography and restenosis was assessed in a number of different ways. In the interest of time I am not going to go through the details. But the bottom line is that we could not find by any measure that we looked at an impact of the IIb/IIIa agent, Tirofiban, on restenosis.

DR. PACKER: Marv?

DR. KONSTAM: I just wanted to make another comment or two about the endpoint timing issue. Actually, I am not at all enamored with the 30-day time point either because if the purpose were really to say have we significantly altered the natural history for this patient, really, we would like to go at the six months or a year routinely. And the 30 days is in fact not all that exciting. So why don't we just do all of these studies at a year. I think that the reason that we do not do them all at a year is because, as we have been saying, you know, there is a lot of other noise entering in as you go through and,

therefore, it becomes harder, and harder, and harder to show the effect and you have to do bigger, and bigger trials. Now, maybe we should do that. But, if we do not want to do that, then we are reduced to saying, well, what can we impute from the studies that we can do?

My own feeling about it is that I am pretty satisfied with looking at 48 hours or 24 hours in a drug where that is the time course where I expect the drug to act, as long as I am pretty convinced by everything that what we are not seeing is simply a shift in the kinetics of the events, and that is to say that is what is really going on is the reason we are seeing fewer events at 24 or 48 hours is because we have just delayed the events a few days or a few weeks. I do not know how we are ever going to completely know that without looking at a year. But I think that as the -- and this is I think Bob's point, that as the entirety of the data start rolling out, as we start seeing all of these studies, as we start seeing all of these curves, I begin to get fairly reassured that what we are seeing at 48 hours is not simply a shift in the kinetics of events, but actually represents the drug doing something good, you know, while it is being administered. So that is my comment.

DR. PACKER: Ray.

DR. LIPICKY: Just one quick one. It strikes me

that it would be okay to view this as a drug effect that occurs early and one looks where the light is because that is where the light is. What one wants to be assured of is that something bad does not happen later. It is how you can be sure of that that has not been very well defined at the moment. But it is not much different than blood pressure.

DR. PACKER: I think --

DR. LIPICKY: I take that back.

DR. PACKER: I do not think that we should talk about that.

[Laughter.]

DR. PACKER: It will -- another time, another day.

Okay. Just one statement. A lot of -- I guess that this has been conventionally referred to, that is RESTORE, as a PTCA trial. In all fairness, this is an unstable angina/non-Q-wave MI trial in which all patients happen to have PTCA. The timing of the intervention was dictated by the procedure.

DR. SAX: This is a trial of patients with acute coronary ischemic syndromes, unstable angina, non-Q-wave, and Q-wave infarction who underwent angioplasty.

DR. PACKER: Okay. Bob?

DR. TEMPLE: Can I ask the sponsor what you think RESTORE supports?

DR. SAX: We believe that the RESTORE trial

supports the use of the drug in the setting of angioplasty.

DR. PACKER: I could not hear you. Sorry.

DR. SAX: I am sorry. We believe that the RESTORE trial supports the use of the drug in the setting of angioplasty.

DR. PACKER: Okay. We will hold that for a moment and ask you to continue with -- Dr. Sax, why don't you continue all of the way to the end.

Agenda Item: Drug Safety

DR. SAX: I am actually just now going to briefly review the safety for the drug. Let me discuss the three aspects of safety, bleeding complications, thrombocytopenia, and non-bleeding adverse events. The main concern with an anti-platelet agent especially when used in combination with an anti-thrombin such as heparin of course will be bleeding. Overall, in the program there was an increased risk of bleeding events when Tirofiban, especially when Tirofiban was added to heparin. But the vast majority of these events, which were meticulously documented, I might add, were either oozing or mild bleeding primarily at the catheterization site or mucocutaneous sites. The latter is what one would expect from a potent anti-platelet agent.

By definition, the way that the bleeding events were defined, these events, these mild events and oozing events were not considered to be clinically significant.

Let me turn now and show you the major bleeding events for the unstable angina trials first.

First, the PRISM trial which provides a good estimation of bleeding for the drug alone, as well as I might add, the overall safety of the drug alone.

Because PRISM did not include procedures and focused on medical stabilization, the overall rate of major bleeding was quite low, 0.4 percent for TIMI major bleeding in the Tirofiban and the same rate, 0.4 percent, in the heparin group. In particular, there was a low rate of intracranial hemorrhages, which was 0.1 percent in each group.

TIMI minor bleeding in the study was also low, two percent, and 1.9 percent, and so essentially comparable between the two treatment groups.

There was a low rate of transfusion, 1.9 percent versus 1.2 percent, representing overall an excess rate of transfusion of only 0.7 percent in patients receiving Tirofiban alone.

Now, PRISM-PLUS, as you recall, was the study where patients received Tirofiban plus heparin. And you will recall, again, that 90 percent of these patients underwent angiography and also that the drug was given for on average for three days. Even after this continuous infusion, the rate of major bleeding was low, 1.4 percent in

the Tirofiban plus heparin group, versus 0.8 percent representing only a 0.6 percent excess of major bleeding. There were no intracranial hemorrhages in the study.

There was a slight increase in TIMI minor bleeding, 10.5 percent, versus eight percent. But this translated only into a 1.2 percent excess of transfusions over the course of the study period in patients receiving combination therapy.

So, if I could summarize this, this represents about one excess transfusion which is a low rate especially considering that there were five cardiac ischemic events prevented at the same time point.

I think that the RESTORE trial was of particular interest though because this represents the highest dosing regimen of Tirofiban given with the highest doses of heparin in the setting of an arterial puncture. Even in this setting, the rates of major bleeding are quite low, 2.2 percent in the patients receiving Tirofiban plus heparin, versus 1.6 percent, an excess rate of 0.6 percent, and the rates of intracranial hemorrhage in the study. This represents one patient. We are also quite low and very much in keeping with what has been seen in these types of studies with other agents.

There was a higher rate of TIMI minor bleeding, 12 percent versus 6.3 percent. But, again, the excess rate of

transfusion was only 1.6 percent in this setting of high doses of heparin and the dose of Tirofiban with arterial punctures.

So I think that one can say that overall, even with this regimen, the drug was generally safe with only a modest excess of bleeding that required transfusion. I think, again, that these data support the use of the drug in the setting of angioplasty.

Let me turn now to thrombocytopenia, which has been reported with all of the IIb/IIIa agents as well as with heparin. The rates of thrombocytopenia defined in this program as rates of less than 90,000 platelets per millimeter squared were quite low for patients treated with Tirofiban -- 1.1 percent in PRISM and 1.8 percent in PRISM-PLUS, and 1.1 percent in RESTORE. This represents when one looks at these numbers only a 0.6 percent excess of thrombocytopenia versus heparin which, as I mentioned, has its own known rate of thrombocytopenia.

In all of these cases of thrombocytopenia, the thrombocytopenia resolved within four to six days after cessation of the study drug and occurred without any major clinical sequelae. In cases of moderate thrombocytopenia defined as less than 50,000 or severe thrombocytopenia defined as less than 20,000, you can see that the overall rates of thrombocytopenia were quite low. In fact, for

patients less than 20,000, there were only five patients in the entire program who will reach this level, and all of these patients recovered from their thrombocytopenia within four to six days of stopping the study drug without any major clinical sequelae.

Late thrombocytopenia that was related to the study drug was not apparent in the program.

Finally, with respect to safety, there were no major differences between the groups in the overall rates of non-bleeding adverse experiences, drug-related, non-bleeding adverse experiences, discontinuations due to non-bleeding adverse experiences, and serious non-bleeding adverse experiences.

These findings suggest that the drug was generally well-tolerated with the only important drug-related adverse experiences being the bleeding at a very low rate of thrombocytopenia. Again, the low rates of major bleeding and the low excess rate of transfusions over standard care, in light of the reduction of cardiac morbidity we believe equates to an acceptable benefit-risk profile for the treatment of patients with unstable angina, non-Q-wave infarction.

So, let me summarize the clinical program by saying that we have studied the efficacy and safety of Tirofiban in over 3,800 patients who actually were treated

with the drug. Through medical stabilization as part of the overall treatment strategy and through angioplasty a drug effect could be demonstrated with an acceptable safety profile.

The key conclusions of the program are as follows. First, the PRISM-PLUS study I think convincingly shows that the combination of Tirofiban with heparin reduces cardiac ischemic events, especially myocardial infarction even before procedures take place.

The finding of a clinical benefit before procedures is supported by a reduction of thrombus burden linking the pathophysiology with clinical outcomes. Importantly, as the drug is continued through a treatment strategy which includes angiography and angioplasty, the benefits of combination therapy for the early management of unstable angina are clearly evident, including a reduction of a combined endpoint of myocardial infarction and death.

The results are robust and consistent across subgroups, including whether or not patients are medically managed or undergo revascularization.

Finally, these early benefits were maintained through 30 days and through six months.

Second, the PRISM trial demonstrates that Tirofiban alone without heparin further reduces early cardiac ischemic events during the medical stabilization

period compared to an active control, mainly heparin.

Third, the prospective angioplasty trial RESTORE, in which Tirofiban plus heparin was initiated at the time of angioplasty supports the safety and clinical efficacy of Tirofiban in patients with unstable angina, non-Q-wave MI to undergo this procedure.

In all of the trials there was a low incidence of major bleeding even in the setting of invasive procedures and a low excess rate of transfusions. So, overall, Tirofiban, in combination with heparin provides both short and long-term benefit with an acceptable safety profile to patients with unstable angina, non-Q-wave MI. We believe the findings of these three trials support the indication we are seeking which is that Tirofiban, in combination with heparin is indicated to prevent cardiac ischemic events in patients with unstable angina, non-Q-wave infarction, including those patients in whom coronary angiography and angioplasty or atherectomy are clinically indicated. Thank you.

Agenda Item: Questions and Answers

DR. PACKER: Any questions from the committee on this last part of Dr. Sax's presentation? Udho.

DR. THADANI: I might have missed it. There was, in one of the trials there was some retroperitoneal hemorrhages. Was that counted as a major bleeding or minor?

DR. SAX: Retroperitoneal -- the TIMI classification does not specify retroperitoneal hemorrhage specifically as a criteria. But generally the patients who had retroperitoneal hemorrhages would also have major bleeds that would be classified in the TIMI classification.

DR. THADANI: Am I right in saying that there were six and three? I cannot remember off-hand in one of the trials, wasn't it, related to --

DR. SAX: Yes. In the RESTORE trial, which was the only trial where there was a slight excess of retroperitoneal hemorrhage in PRISM and PRISM-PLUS. The rates were very low and there was really no excess. In RESTORE, the rate was 0.6 percent in the Tirofiban plus heparin group versus 0.3 percent in the heparin placebo group for retroperitoneal.

DR. THADANI: Was it a Realpro or something? Because, you know, in the PRISM-PLUS you had a longer duration of infusion and here is a shorter duration and yet we are seeing something. Are the procedures different or other drugs were used? Just curious.

DR. SAX: I am sorry, could you --

DR. THADANI: Was Realpro used more often?

DR. SAX: No. There was no Realpro use in the RESTORE trial, no.

DR. PACKER: Okay.

DR. KONSTAM: Rick, in our experience with it with another, like a protein IIb/IIIa inhibitor, we have seen a number of cases of pulmonary hemorrhage that might not readily have been interpreted as such, respirator distress, abnormal chest x-ray. And then only with time it became evident or a little bit further investigation it became evident that the infiltrate represented a pulmonary hemorrhage. I just wonder if you have anything in your database to suggest that there might be something similar going on with Tirofiban?

DR. SAX: We can no that we have not seen that.

DR. MOYE: I have just a hypothetical question for either Ray or Bob. Let's say we have two drugs, one is called Quickstatt, and the other is called Longstatt. Quickstatt has an efficacy benefit shown at 48 hours, but not at 30 days. Longstatt shows a benefit at 48 hours and 30 days. Let's say that everything else is equivalent in its hypothetical construction. Is there any difference in labeling. I assume that they are both approved. Is there any difference in labeling?

DR. LIPICKY: Well, we have come to you with just that circumstance so that you can tell us what to do.

DR. MOYE: Okay. Thank you.

[Laughter.]

DR. PACKER: That is why they brought us here.

DR. LIPICKY: I am sorry. Dr. Temple does have the answer.

[Laughter.]

DR. TEMPLE: I do not have the complete answer, but they was definitely a big difference in labeling. You would state what was found in either case. It is possible that both might be considered approved. Both might be approved. But the one where the effect held on to 30 days would be able to say that and the one that did not would not and would have to describe what occurred. So there would be a difference even if you thought that both of them could be approved.

Now, could one of them say that I am better than you because I did this? That is a trickier question. They might be able to say that we showed this and no one else has and things like that. So there can be differences in labeling and promotion.

A different question is whether they can both be made available.

DR. PACKER: With that in mind, we are going to take a 10-minute break.

[Brief recess.]

Agenda Item: Committee Discussion and Recommendations

DR. PACKER: Tirofiban inhibits the binding of

fibrinogen to the platelet IIb/IIIa receptor thereby inhibiting platelet aggregation and clotting. In this respect, it is similar to -- I have never been able to pronounce this F5FI (sic). Not bad.

Integrin, which the committee discussed at the meeting of January 28th. Merck proposes that Tirofiban be approved for use in combination with heparin to prevent cardiac ischemic events in patients with acute coronary syndrome and non-Q-wave myocardial infarction.

There are three major clinical trials called RESTORE, PRISM and PRISM-PLUS. You can read the regimens used in these trials.

The first question to the committee which we will ask our primary reviewer to address first, the first question is do these regimens have the same effect on platelet aggregation? Dan?

DR. RODEN: I am not sure about the RESTORE regimen because of the quick but high-dose bolus. The others, certainly the two PRISM Tirofiban doses have the same effect. The lower Tirofiban dose I think was a little bit on the lower end of the dose response curve, but still, not quite at the flat part, but sort of toward the top of the flat part.

The bolus I am not sure about and the maintenance infusions obviously do.

DR. PACKER: I guess we did not actually see any specific data about the bolus at all. Rather than ask for that information, we would simply ask the division to reassure itself that data exists on the bolus to justify the concept that its platelet -- anti-platelet effects are similar to the other regimens that have been utilized. Are there any other comments from the committee?

[No response.]

DR. PACKER: A second question. Can you describe the time course of platelet aggregation/inhibition when Tirofiban is administered according to any of these regimens?

DR. RODEN: Rapid onset, maintained after rapid onset.

DR. PACKER: Okay. I do not think that anyone disagrees with that.

The next questions deal with specific discussions about the individual trials. The order is PRISM, PRISM-PLUS, and RESTORE. I am not going to read the description of these trials. We have already spoken to the issues about the design endpoints and statistical analyses.

The first series of questions deals with PRISM. The first question is did all three components of PRISM's primary endpoint contribute to its results? Please remember the primary endpoint in PRISM was death, non-fatal

myocardial infarction and refractory ischemia within 48 hours of starting the infusion. Dan?

DR. RODEN: Just getting my notes out. The answer is no. No, no, the combined endpoint in PRISM was the 48-hour endpoint which was significant to the .014 level. It is driven almost exclusively -- that is the level of significance that is driven almost exclusively by recurrent ischemic events. MIs were -- the P value was .19. And death at 48 hours was .54.

The MI numbers drifted into the same direction with the same sort of extent of reduction as the recurrent ischemic events. There were very few deaths. There were six versus four, and they were in the wrong direction. If one wants to take reassurance in small numbers, then the deaths at 30 days which actually reached statistical significance were 37 in the Tirofiban group and 59 in the heparin group for a P value of .021.

DR. PACKER: Okay. Dan is suggestion that, in fact, most of the driving force for the primary endpoint is the effect on recurrent ischemia. Does anyone disagree with that?

[No response.]

DR. PACKER: Okay. The results of PRISM on the primary endpoint are listed at the top of page two in the framed box both at the two days, seven days, and at 30 days.

Please remember the primary time for analysis was at two days. The committee has already during its deliberations this morning spoken to a number of issues related to the analysis of PRISM and I guess particularly the adjudication of events and a number of these statistical issues that were discussed.

Taking all of what you heard this morning into consideration and thinking only of PRISM alone -- and I want to emphasize both of these points -- putting everything that you spoke about with PRISM this morning and viewing the responses of the sponsor, but only considering PRISM, do you think that the results of PRISM, in terms of its utility in patients with acute coronary syndromes are: A, probably attributable to chance, B, plausible, but weaker than those in the typical successful trial, C, as persuasive as the findings of a typical successful trial, D, more persuasive than one trial but less persuasive than two trials, or, E, as persuasive as two or more typical successful trials?

Now, this is a format that the committee has utilized before in order to gauge our level of confidence in the results of a single study. Dan?

DR. RODEN: Just to amplify what my view of the question is. If we all answered E then we could vote on approvability now and go home.

DR. PACKER: No.

DR. RODEN: But we will not. We would still answer the rest of the questions. Right, no. I understand that. But that would be the implication of a vote for E. A vote for A would be that we did not think that the drug did anything. I find that the results of PRISM are as persuasive as the findings of a typical successful trial.

DR. PACKER: Okay. Can we have discussion about it? We are not interested in votes now. We are interested in a discussion. Udho?

DR. THADANI: I think a couple of reasons. We discussed at length, although the primary endpoint is at 48 hours, one will have to attach some significance to day seven and day 30, which to me is somewhat not reassuring. I would like to see the benefit to persist at least a week or 30 days. So that lowers my confidence, although the trial is positive at its primary endpoint or by that. I have got some reservations on that. Since it is driven primarily by ischemic endpoints and there is even, if you combine ischemic endpoint, it is negative at day seven and 30. I think it is a weaker trial. I am favoring for B rather than for C for that reason.

DR. PACKER: Jeff?

DR. BORER: Without coming down on a number and a letter yet, one of the things that I think we have to consider in dealing with PRISM is what is the comparator?

It is heparin and how we feel and believe about the importance of this trial and the implications of this trial depend in part on what we think of the efficacy of heparin. Heparin is not approved by the FDA for the indication for which it was used in this trial. Certainly, the data that would support heparin use are not as rigorously defined as they would be for an approvable drug which does not mean that heparin is not any good. You know, there are a lot of positive data.

When I look at this trial, I see that the study drug did better than heparin at 48 hours and sort of was moving in that direction at the later time points. If I think that heparin is a reasonable drug than that gives me some reassurance.

All of that having been said, I think that, as a single indicator of the efficacy of this drug for patients with acute coronary syndrome, without additional data, I would find this plausible but perhaps a little weaker than those of the typical successful trial because of my lack of assurance about the comparator, but maybe just a little bit more than plausible, so between IVb and IVc.

DR. PACKER: Okay. Jeff, just to explore what you have said, this committee has in the past seen a number of trials that have been comparative in nature. Sometimes we know for sure that the comparator works because it is

approved and there is a big database. And then we have seen trials where there is a comparator that clinicians use which may or may not work or that it is not approved, and more importantly that the data supporting its use may not necessarily be persuasive.

The way that sponsors have handled the first situation in the past is actually to calculate the treatment effect and the confidence intervals, and allowing for the identification or calculation of a putative placebo, which in this case would be almost impossible to do because the database is inadequate.

So, I think that what you are saying is that you are reassured a little bit by the fact that it is a comparator is something that you feel relatively comfortable with, but it is impossible to do any calculations based on that feeling.

DR. BORER: That is absolutely right. More than that, there is not -- or as a corollary to that, there is not the large database that I could look to to be absolutely certain that heparin really is effective in this particular population, although I think that it is.

DR. PACKER: Jeff, could you clarify that a little more.

DR. BORER: There is nominal significance early. That is not against placebo, but against something that may

well be active. I guess I would have thought to the extent that we believe heparin is active that would have moved you down the letter grade, but it moved you back. Why is that?

DR. PACKER: Down the letter grade means a better letter.

DR. BORER: Moving toward D and not toward B. But you moved toward B.

DR. PACKER: The question here is the utility of Tirofiban in patients with acute coronary syndrome. I would sort of -- I have to interpret that question because I think that it is not complete. It is the utility of Tirofiban in patients with acute coronary syndrome for what? If the what is to get us to the next step, well, you know, I think that we do not have the data here that would support, in a rigorous way, that we necessarily get to the next step, but the total patient management is positively impacted by this therapy. That is not to say that it is not because we have PRISM-PLUS to look to to ask that question of. But PRISM alone really does not provide data about that. So, if we look at PRISM in isolation, yes, it is better than a drug that I think is active and certainly is not -- there is no data to suggest that heparin is bad in this situation. So the fact that it is better than heparin at 48 hours is very reassuring at 48 hours, but I just do not think that those data by themselves are sufficient to tell me with absolute

certainty that the drug is appropriate for patients with acute coronary syndrome. Added to some other data, it might be very persuasive however.

DR. TEMPLE: As Milton said, the question here is as much as one can do it. It is a little artificial. But looking at it as an individual study, is it a sort of regular study with the usual P value, stronger than usual, less than usual? I was just focusing on the one point you made which is that the control is not placebo, but a drug that you have some beliefs about. I want to know the influence of that fact.

DR. BORER: Looked at as a study, as opposed to for the utility of the drug in patients with acute coronary syndrome, but as a study that set out to show a certain thing, do I think it showed it with this comparator, yes, it did.

DR. PACKER: Marv?

DR. KONSTAM: It seems to me that we have to separate out the two different questions of the strength or validity of the trial in reaching its particular endpoint and whether it is convincing in that regard on the one hand, and, on the other hand, this discussion that we have been having about what is the most appropriate time endpoint because I think that they are sort of different questions.

I think, in my reading of this trial, it is pretty

clearly a positive trial. It met its primary endpoint. I am actually more reassured than dissuaded by the fact that there is at least a strong trend to hold on to that effect later on even though it loses its significance.

I think that when we get to the issue of how do we interpret this positivity, that then gets to the different question. I think that when we get to that question then we really have to bring in the entirety of the data set about what we think is going on here. What do we think it means that an endpoint is positive at 48 hours and reach our own conclusions about that. I am convinced enough that there is not a fall-out from all of the data, that there is not a fall-out going on beyond the 48 hours that I am pretty accepting of the 48-hour time point. But, as far as the trial is concerned, I think that it is a positive trial.

DR. PACKER: How concerned is the committee about the fact that the driving force, as Dan and the committee agreed, is the softest of the three endpoints and that this process was one investigator -- that it was adjudicated, it was adjudicated in a very reasonable fashion and some of the issues related to that have been addressed. It is still the softest of the three.

We can put a small amount of concern on that, or moderate, or big depending on individual preferences of the committee. How big is that? It is relevant. The intent I

think is not necessarily to answer that question right now because there is a specific question to the committee about that. But it might be appropriate when you vote on this to take all of the issues that you have heard into consideration. That might include the concerns raised by time points or by the driving force to the primary endpoint or it could be reassurance gained by the fact that it is heparin and not a placebo. Please, factor all of this into consideration when you vote.

DR. MOYE: The question that is asked, the balance point is 4C. The question is are the findings as persuasive. That is not asking whether the trial is positive or not.

DR. PACKER: Right.

DR. MOYE: So it is asking us I think to fold in some of these concepts that you have mentioned.

DR. PACKER: Right. Please, remember, Lem, I want to emphasize that. If the only question that we were being asked was did this trial meet its pre-specified endpoint, you do not need a committee to do that. You need a computer that you plug in what the critical alpha level is. You see with the primary endpoint achieved a P value smaller than alpha, and you come out with an answer. That is not what the committee is being asked for. It is being asked for a judgment.

Okay. Let's vote on this.

For purposes of trying to simplify the process, I would ask the committee not to vote between B and C because B, by definition, is less than C. So, if you think it is between B and C, please vote B. It just makes everything so much simpler.

[Laughter.]

DR. PACKER: Okay. Marv, why don't we begin with you?

DR. KONSTAM: I will vote C.

PARTICIPANT: B.

PARTICIPANT: B.

PARTICIPANT: C.

PARTICIPANT: B.

PARTICIPANT: C.

PARTICIPANT: B.

PARTICIPANT: C.

PARTICIPANT: B.

DR. PACKER: What was that vote? Six B and three C. Okay. Let's proceed.

PRISM-PLUS is the next study under consideration. The description is well-known. The primary endpoint was death, non-fatal myocardial infarction and refractory ischemia.

Joan needs to have this for the official record.

Can all of those who voted C please raise your hand?

[Show of hands.]

DR. PACKER: So it is six to four. We were just missing one vote.

The primary endpoint of PRISM-PLUS -- death, non-fatal myocardial infraction, refractory ischemia within seven days. The questions are very parallel to those for PRISM. Dan did all three components of PRISM-PLUS, contribute to the primary endpoint.

DR. RODEN: I am looking at the data now. My sense was the same.

DR. MOYE: I thought that the MI and the ischemic episode were concordant, but that perhaps death was not. There were so few cases of mortality.

DR. PACKER: Lem, the descriptor --

DR. RODEN: Sorry about that. So, the P value for the -- this is for the Tirofiban plus heparin, versus heparin alone. We will have a discussion of what happened to Tirofiban alone in this trial later.

So the P value is .004, driven by a hundred events in the treatment group and 143 in the comparator group. Recurrent ischemic events and MI both reached statistical significance when looked at alone. In fact, the MIs are almost half in the treatment group. The deaths are very small and actually exactly equal at the specified primary

endpoint.

So the answer to the question is that it is driven probably in this case both by recurrent ischemic events and by myocardial infarction, which includes both fatal and non-fatal myocardial infarction. Most of the myocardial infarctions were non-fatal.

DR. PACKER: Does anyone disagree?

[No response.]

DR. PACKER: Okay. The next question is -- and it is exactly parallel to the question in PRISM -- looking at PRISM-PLUS only and taking into consideration all of the discussion that you heard today, you are being asked for an interpretation of the results in PRISM-PLUS. So please take into consideration everything that you know about this trial. Do not simply focus on the P value for the primary endpoint. Do you believe that the results of PRISM-PLUS are: A, probably due to chance, B, weaker than the typical successful trial, C, equivalent to one trial, D, between one and two trials, and, E, two or more trials.

DR. THADANI: Before you vote I think that you should separate out --

DR. PACKER: I am not voting. There is no voting.

DR. THADANI: No, no. But you should separate out the three limbs of the trial because there are three limbs as it is on the table. I think that you should separate out

the Tirofiban alone versus heparin, or the combination versus heparin. I think that that would be very relevant, otherwise, it would be a totally confounding issue because we already voted B and C in the last one. I think that we should probably separate out one component and vote on that and then go on to the second component.

DR. MOYE: One of the arms was discontinued, right?

DR. THADANI: I realize that, but it is still not clear on the question.

DR. PACKER: Udho, let me suggest that there is a subsequent question that really deals with that. It is much later on. It deals with Tirofiban alone.

DR. THADANI: We just restrict it.

DR. PINA: Maybe this question should say Tirofiban plus heparin.

DR. PACKER: Tirofiban plus heparin. Let's just try focusing on Tirofiban plus heparin versus heparin or versus placebo and heparin and focus on that. Dan, what would you propose?

DR. RODEN: Well, the issues are really very similar to the last time. The question of heparin as a comparator, as opposed to a pure placebo -- okay, so this is a truly placebo-controlled trial as opposed to an active control trial if you throw out the Tirofiban arm. The

Tirofiban arm bothers me. Okay. I have said it. On the other hand, the statistical significance reached is more than one would -- certainly much less than .05. That is not driven by only a single softer endpoint. It is driven by a somewhat harder endpoint, myocardial infarction.

This is the trial that sort of goes on the longest. It does not have the largest numbers. So when all of that dust settles about the pluses and the minuses, I come down between 6C and D and I will come down at C.

DR. PACKER: Okay. We are going to have a general discussion. Remember, right now you are not voting. Lem, why don's you begin the conversation on this.

DR. MOYE: I am a little more enthusiastic about PRISM-PLUS than I was about PRISM for two reasons. The first, unlike PRISM, where the repository of the effect resided in the weakest component of the endpoint, we really see some more concordance, particularly in the finding for efficacy in the MI. So I feel a little bit more comfortable with the presentation of the components, of the primary endpoint, and how they support the overall P value at the seven-day timing.

Also, and perhaps just as important, if you look at the time course of efficacy beyond the primary endpoint, you know, it tends to persist to 30 days and, even to some extent at 180 days. I have been very much concerned about

the findings of efficacy very early in trials with a notable lack of efficacy shortly thereafter. But that is not the case here in PRISM-PLUS. So I feel somewhat more enthusiastic about this trial.

DR. PACKER: Ray.

DR. LIPICKY: And the fact that if you take the investigator opinions and look at what that gives you for a P value for the primary end point and it goes to non-nominally-statistically-significant trial, does that enter into your thinking process at all?

DR. MOYE: Yes, it does. And it obstructs me from saying it is more persuasive in the findings of a typically successful trial. It keeps me from going down to D. But I think that given that the investigators said that they were going to be committee- adjudicated primary endpoints, then I tend to give that finding much more weight than I give the investigators.

DR. PACKER: Tom.

DR. GRABOYS: I am increasingly enthusiastic as we move from a soft to a hard endpoint. MI I think is an important element and kind of moves you down the alphabet. But at the end of the day the bottom line is that I want to see who is alive and who is dead. I think that all of our collective enthusiasm would be if we could show that we had a saving of lives.

DR. PACKER: Is that really true, Tom? That is really the only thing that matters in life is whether you are?

[Laughter.]

DR. GRABOYS: Well, you know, you are dead a long time.

DR. THADANI: That is not a philosophical issue because life or death could be important in this context because you are measuring infarcts with small enzymes. I think that becomes a very relevant issue. If you are not left with any permanent disability like heart failure or you are coming back with recurrent angina, I think that it is a very relevant issue how many bodies you can count, if they are functioning normally. If you are just diagnosing infarct by small bumps in enzyme, unless you could show prognostic significance which should show up on say month six or 12, then I think that his point is very valid. We cannot laugh it off. Obviously, if it leaves a permanent disability than it is a different issue. The data even on small CPK pumps is driven from the Duke database. Other trials are not showing positives. I think his points are well-taken.

DR. PACKER: Let's just try to clarify this because it has implications not only today but implications generally.

In the past this committee has seen a fair number of trials with a combined endpoint of death from MI. I guess I have heard this committee say that death and MI seems to be reasonable because to require an effect on mortality to be persuasive may not, one, be realistic given the number of events, and, two, may not be clinically appropriate given the fact that bad things can happen to people which are non-fatal.

On the other hand, Udho says that, well, maybe some of these bad things that happen to people which are non-fatal are really more biochemical phenomenon and not necessarily clinically-relevant phenomenon. I guess that you would be more reassured if you knew there was less cardiogenic shock, or a heart failure, or other things that would be the clinical consequences of an acute myocardial infarction.

But, in general, this Committee has taken the position that an MI is an MI. Sometimes we have actually gotten into -- we have seen sponsors get into trouble when they try to micro-manage the definition of MI which occurred with Integralin.

DR. THADANI: No. Do not take it out of context. Nobody is saying MI is good for you necessarily. Again, the data collection becomes very critical. If you are going to do it, you do serial enzymes for X, Y point in time. In

PRISM I think that they did a good job. The trial is positive. Nobody is saying that the trial is not positive. I think that it is positive. It is not driven only by an ischemic episode, but also by enzyme measurement of MI. The deaths really did not change which is reassuring that at least not more people have died in the other group. I am not saying that. All I am just saying is that if really the small infarcts in the long run -- say that there are a lot of episodes happening because you are doing a lot of intervention, it should somehow translate down the road. So I think that you have to take the totality of the data not only at day seven, day 31, day 180, perhaps one year is important to solve those issues. I am not saying in this trial --

DR. PACKER: But what would you be measuring at 30 days or at six months or a year?

DR. THADANI: All you could do is rehospitalization and death. That is all you could do probably for unstable enzyme. It is a very positive trial. All I am just saying is say that -- suppose CPK bump by definition is twice normal, versus sometimes three types normal. I am not sure that there is that clear database, you know, spontaneous CPK bump or twice is as bad versus post-angioplasty bump of three times. All I am doing is just raising some issues. I am not saying that they did

anything wrong. The trial stands as it is.

DR. PACKER: Okay. Let's try to do this. I think that this is an issue that easily could consume this committee for a very long time. Let me just remind the committee that the sponsor, in its follow-up period of 30 to -- 30 days or six months did include rehospitalizations for unstable angina which is concordant with your recommendation, Udho. So that was actually done by the sponsor. So, can we stick to the actual question?

Ileana?

DR. PINA: Yes. Dr. Sax made a point at the beginning of his presentation that the population may be a little bit different between PRISM and PRISM-PLUS, and that PRISM probably encompassed more patients who had previous known coronary disease. So, we may be talking about two different populations here. But the number of deaths are so small in both groups that I cannot make any judgments about death. But myocardial infarction to me is a very hard endpoint, and it is positive. I mean, it is real. It is there even when the committee met. I do not think that you can deny that.

DR. GRABOYS: I am not diluting the importance of MI. That is not even an issue. My statement about death was philosophic as well as those issues because that is what I want to see. I think that all of us would.

DR. PACKER: The question is how disappointed are you when you do not see it?

DR. GRABOYS: Well, I am disappointed enough that I am not moving -- I am going from 6E down to 6C.

DR. PACKER: I understand. Marv?

DR. KONSTAM: Well, since Rob Califf is not up here and sitting in the back, I mean, I will have to make the point about hypertension and say that we routinely approve drugs for treating hypertension. I would say that if I had to choose between having hypertension and having an MI I would probably choose hypertension. I mean, I think that MI is pretty good -- I mean, if the only thing that matters, of course, is survival and quality of life, those are the only things that are important, I think that we can accept MI as a bad indicator of those other bad things going on down the road.

I am more sure about these MIs than the MIs that were looked at in the Integralin database because these are MIs that it sounds like, for the most part, were identified and diagnosed by the investigator and then confirmed by the events committee, as opposed to MIs that were sort of detected by the events committee in the absence of any concern on the part of the investigator. So I think that these are the kind of MIs, although some of them may be small, that we actually know something about based on reams

and reams of data about the natural history following MIs. Those other MIs I am not so sure that we know very much about.

The only other point that I wanted to make was that I actually just, in terms of answering this question, I think that it is a very, very strong study for all of the reasons that people have said, looking at the Tirofiban on top of heparin versus heparin alone story.

I am worried a little bit still about the dropping of the Tirofiban group alone partly from a statistical sense. Maybe Lem can reassure me or somebody else. I mean, we have seen before three limb studies where an interim analysis showed something ugly in one of the limbs, say the Data and Safety Monitoring Board said let's bet rid of that, and you are left with a very positive result in one of the other limbs. Are we really reassured that that issue is taken care of by the routine way of adjusting the nominal P value here? I am not sure exactly what I am asking. I am disturbed about the fact that this is a three-limb study that has suddenly now become a two-limb study based on that initial analysis and how much that should denigrate our excitement about the positive finding in that one limb.

DR. MOYE: In one sense, we are off-the-hook from really pursuing a rigorous answer to that question by the low P value that they have for the primary endpoint. Any

reasonable adjustment that you might make for discontinuing that arm is not going to set the threshold so low that 004 is not going to be significant.

DR. PACKER: I think what Marv is asking is beyond statistics are there -- is there information in the Tirofiban alone arm that should diminish our enthusiasm for the Tirofiban plus heparin arm. Is that what you are saying?

DR. KONSTAM: Well, I do not know if I would say beyond statistics. I guess that I am worried that the typical statistical method of adjusting for a three-way comparison, I am just concerned about what the implication is when an early look finds something bad and, therefore, throws out that limb. I am just concerned as to whether our typical way of adjusting that statistic adequately accounts for that. I mean, we have seen this in other trials where, then with repeat study it came out very different later on. I do not know if anybody has an answer to that.

DR. MOYE: You know, any attempt to try to adjust the P value that you are going to use to assess the heparin placebo versus heparin/Tirofiban group is going to be fraught with difficulty. You might think about something like, well, if I am really more concerned about hazard, maybe my two-sided test should not be symmetric anymore. Maybe I should put more alpha on the side of hazard. But

that is a decision now that it based on an interim analysis in a group that has been discontinued now trying to attach part of that finding to your decision rule for the other two comparators. That is going to be very tough to defend methodologically I think.

DR. PACKER: Yes, Marv. I think that given the kind of experiences you are referring to, it does not sound like it could be handled statistically. I think that it is something that you would factor into the equation.

Ray?

DR. TEMPLE: Well, the other thing is is that the events that occurred -- no, I guess that is not right. I mean, the one thing that one could do is simply see what happens when you pool all Tirofiban groups, including the one that was dropped. That is a relatively small number of events. That would be based on the hypothesis that somehow they are not really different, but it just came out that way. I wonder if that has been done. But, in any event, we could certainly do that. My guess is since the difference is only about 10, it is not going to make much difference in the overall outcome, right?

DR. PACKER: Although the number of total deaths is small, so 10 actually might represent something. Ray?

DR. LIPICKY: I want to change the subject. Is that okay?

DR. PACKER: Yes.

DR. LIPICKY: Okay. I just want to repeat the question that I asked the last time but this time make it in the form of a statement and not a question. I do not expect an answer. What I heard in response to the thing that I said last time I did not quite understand so I am going to start differently. Last January when we looked at Hepthapibatide, when we looked at the primary pre-specified endpoint and its P value, and then look at the investigators' P value, the investigators' value was an order of magnitude more significant than was the CEC's primary endpoint. I found that very comforting.

In this case, it goes in the opposite direction. What I heard you saying is that that comforts you. I did not understand that. You do not have to respond.

DR. MOYE: But I can respond. Of course you would like to see concordance of results. You would like to see the same strength of evidence, the same relative risk regardless of who looked at the endpoint. In clinical trials you do not see that. Sometimes you see the investigator -- but depending on the instructions that the investigators are given, you can see very different results. I guess that it is for that reason, of course, we all know. That is why we try to stick to the primary endpoint because that is the analysis that is going to determine whether we

judge the trial as positive or not assuming that they follow the protocol.

Now, having said that, I can feel more comfortable or slightly less comfortable if things do not all go in the same direction. I do not feel comfortable about PRISM because of the weakness of the primary endpoint, but I am more discomforted by that than I am by the fact that investigators find different things.

Investigators in PRISM, for example, may have felt that it was in their best interest to send almost anything in. They had nothing to lose by that because that way they know, they never get accused of holding on to an endpoint and not reporting it. It is that kind of climate that makes the investigator-determined endpoints very difficult to assess I think. So that is why we stay with the primary endpoint which was the committee adjudicator.

DR. PACKER: Marv?

DR. MOYE: Could I feel better about PRISM? You bet. Could I feel better about PRISM-PLUS, you bet, if the investigator-identified endpoints lined up, but they do not.

DR. LIPICKY: I understand everything you are saying except the direction of your comfort. That is okay. You do not have to explain it.

DR. PACKER: Marv.

DR. KONSTAM: I agree with the implication of

Ray's question. I do not think that I am made more comfortable by the fact that the P value gets higher when you go to the investigators. I just wanted to say that my interpretation of the difference here teaches us something I think about how these endpoint committees should be functioning. It should be, my own feeling, a cleaning up act, as opposed to a digging act. I think that that has a lot to do with the difference of the findings. So, as a cleaning up mechanism, I am not made uncomfortable by the fact that the P value gets stronger when they clean it up.

DR. PACKER: Let me sort of go back to a concept that Ray suggested earlier. We want to move to a vote on this, but I just want to make sure that in doing so that we are considering all issues related to this trial. Because I have heard many members on the committee say different things about this trial. Some have said -- and there has not been any vote, but there is some sentiment that, well, this is as good as one trial and then I have heard some sentiment that says that this is a very persuasive study. I guess that I just wanted to make sure because I think that it is very important that the committee be very internally consistent. I understand that it is a goal that we reach only occasionally, but it is a desirable goal.

When we met in January, we said that in looking at the unstable angina trial for Integralin, which had death

and MI as a primary endpoint at 30 days, we thought that that was -- and that was a huge study, 11,000-patient trial that made its primary endpoint. We said that that was as good as one trial. I just want to make sure that we think about what we said in January unless we want to change our minds when we look at this trial which is smaller and include in it an endpoint which is not death and MI and that is measured at a time point which is earlier than the time point measured in the unstable angina and Integralin trial. So let us make sure that our judgments here are not situationally dependent.

I would like to think that we are being a little bit consistent not only in our judgment but the message that we are sending forward. I just wanted to make sure that we think about that and discuss that in reaching a judgment about the study. John?

DR. DiMARCO: I think that there are two things that I would like to say. Let me start off by saying that I think that this type of refractory ischemia, if indeed it meets their definitions, this is a lot of ischemia, two 10-minute episodes in one hour, that is a lot of ischemia with ECG changes. I see a lot of ischemia that does not meet that criteria. I am not surprised that the investigators sent in some extra that did not meet that criteria.

Now, the problem is, in a composite endpoint,

death is a lot different than two episodes of angina. So lumping them together, particularly in these trials where you have three trials, none of which show any change in mortality, despite the fact that if you add them all together you have got a modest number of deaths. There is no change, as I can see, in mortality. But it may be useful to keep down long episodes of chest pain even if it has no effect on mortality. So the composite endpoint is not -- there are endpoints of unequal weight. Adding them together is sort of annoying. I think that this trial shows that on two non-fatal endpoints the drug had an effect. It did not have an effect on mortality. I think that an eventual labeling might say treatment of these endpoints did not affect mortality.

DR. GRABOYS: Are you saying you are equating the current ischemia with the death? I mean, conceptually, is that --

DR. DiMARCO: No. I am saying the composite endpoint has them lumped together as each event. They have a hierarchy of events. I do not think that they are the same at all.

You put together a composite. It would be nice if you had three very serious things of equal severity that just were not the same. Here we do not. I think that this shows that it has an effect on refractory ischemia as they

define it. If this study shows an effect on myocardial infarction, does not show an effect on death, and the other studies do not show an effect on death.

DR. GRABOYS: So we would agree on the labeling then that there would be a mention that there is no difference in mortality?

DR. PACKER: Okay. We are getting far ahead now. This trial, PRISM-PLUS is before the committee. Let's focus on this trial. We have to consider how persuasive this trial is. The only reason for bringing up what I brought up is that, in an attempt to be consistent and fair in a previous meeting with a very similar agent in the same therapeutic class, we, as a committee, said that that was as good as one trial. That trial corresponds to this trial in this package. The endpoints are different. The time point where the endpoint is measured is different. We just want I make sure that we think about that.

Maybe we are willing to change our minds now. We can change anything that we want. We just want to be able to make sure that we are thinking about this in a coherent fashion.

DR. KONSTAM: Just to point out that the statistical, which you did not include, the statistical finding for the pre-specified primary endpoint is much stronger here than it was in that trial. I mean, that is

another element.

DR. PACKER: But, Marv, that means that if someone -- I guess I must say that I just am not persuaded by that. The reason why is because --

DR. KONSTAM: You do not need to necessarily be persuaded or not persuaded. But it is another point that really needs to be made. Now, maybe you disagree with when the timing of the endpoint is. Maybe when you line up the two studies together they look very similar. But I just throw in another point. I am surprised that Lem is not the one standing up and making this point because he usually does. I think that the primary endpoint as pre-specified is worthwhile because that is the one thing that the investigators are putting all of their alpha on.

DR. PACKER: I am not saying that it is not worthwhile. I am just saying line up pursuit with PRISM-PLUS and tell me whether you think that one trial is more persuasive than the other. And try to be internally consistent in your thinking.

DR. LINDENFELD: No, I think in PRISM-PLUS I think that the absolute event rate is substantially lower than it was in pursuit. Maybe I do not remember right. But I think that there we had, even if you just consider MIs and death, I think that there we had 15 events per thousand saved and here we have more like 30. So I think that not only the --

but the number of events is substantially different.

DR. PACKER: They are also different kind of events.

DR. LINDENFELD: No, I said even if we just used MIs in this study, death and MIs, and throw out the refractory ischemias at 30 days, I think that there is a difference.

DR. TEMPLE: I think that what Marv is saying is that the results actually look almost identical, accept for the matter of what the chosen primary endpoint was. The pursuit chose the 30-day endpoint and the result was a little weaker. If you look at early endpoints in pursuit which was just death and MI, they are much stronger. They are at the 003 level. So a lot depends on how important that particular question is. Well, of course, we put greatest credibility, other things being equal, and when there is no other information, for sure, in the originally-identified endpoint. I guess that one of the things that is going on here is that we are starting to see large quantities of data, and people might perhaps choose to be influenced by what all of those data seem to show. But, if you actually look at the findings, the two results almost sit on top of each other for the same endpoints.

DR. PACKER: Bob, that is precisely my point. I think that that is, in fact, Marv's point. Now the question

is how do you incorporate that into a value judgment as to how persuasive the trial is? Dan?

DR. RODEN: I have a somewhat different view. I am not convinced that these are two similar or absolutely congruent trials. In this trial there is a striking effect on the primary endpoint. There is also a striking effect on what would have been the primary endpoint if they had done pursuit. It is more striking, as I recall, than the statistical significance achieved in that very, very large trial, number one.

Number two, if we are going to compare those two trials, we have a clear sense here that the dose chosen to be studied was the dose that was appropriate to have been chosen to be studied. I do not have that sense from the other discussion that we had at the end of January.

And then the third thing that reassures me somewhat, although the numbers are small, is the point that I alluded to before. In this trial, there is a 30 percent benefit or a 30 percent reduction in endpoints among patients who undergo revascularization, total endpoints among patients who undergo revascularization. There is a similar 30 percent or so reduction in total endpoints in patients who actually do not undergo revascularization. The numbers for the latter group are very small. But the fact that they are very, very similar is reassuring to me. One

of the issues that we discussed and actually never came to closure on at the end of January was the question of whether the entire result in pursuit was driven by a beneficial effect in patients who subsequently went on to get or who got -- and Bob is shaking his head, but, in fact, at the time we were here, Bob, the discussion was very clear, and the implication was very clear that the benefit for that particular compound was being driven by patients who underwent procedures.

Now, if a subsequent reanalysis by the agency or the sponsor has shown something different, so be it. But at the time that was one of the things that drove at least my decision to vote the way I did then. And that is why I think that this discussion anda that discussion are not the same thing and that trials are not the same thing.

DR. PACKER: Dan, without revisiting, clearly, revisiting history because every drug package is very, very different, if we compare the two trials in the only way that we actually can, which is to look at death and MI at 30 days, both the magnitude, as well as the significance of that treatment effect is super-imposable between the two studies.

In fact, if one wanted to look at this purely technically, and I really would not want to look at it technically, but, if one wanted to, one could say that at

least pursuit achieved significance on death and MI at 30 days and PRISM-PLUS did not. Its P value is point 025 for purposes of comparison. Ray?

DR. LIPICKY: I think people are taking the comparison too literally, Milton. You do not really want them to compare trial by trial. You just want to sort of have them, as they are saying what they are going to say about A, B, C, D to remember the criteria that they used last time and not to use a different set of criteria, and it is not sort of lining the numbers up and see if they superimpose or reject the Kaplan-Meier curves.

DR. PACKER: That is exactly what I am saying. I think that the idea is not to be married to the P value. What is being asked here is literally a judgment call.

Let's take a vote on this. One has A, B, C, D, E in front of them. Ileana, we will begin with you.

DR. PINA: I will vote C.

PARTICIPANT: C.

PARTICIPANT: Excuse me? You said E?

PARTICIPANT: C.

PARTICIPANT: C.

PARTICIPANT: C.

PARTICIPANT: C.

PARTICIPANT: C.

PARTICIPANT: C.

PARTICIPANT: C.

PARTICIPANT: C.

PARTICIPANT: C.

PARTICIPANT: C.

DR. PACKER: That is maybe one of the first unanimous votes we have had in a long time.

We are moving to RESTORE. The questions are identical. Please remember that RESTORE the endpoint, primary endpoint death, non-fatal myocardial infarction, and repeat interventions for recurrent ischemia.

The first question to Dan. Did all three components contribute to the primary endpoint?

DR. RODEN: Well, the facetious answer is since the primary endpoint was not reached, the question you are asking is irrelevant. However, combined endpoints at other times were reached. So, for example, at 48 hours, there is a nominal value of P equals .003. That is not the pre-specified primary endpoint. But the components that drive that appear to be repeat PTCA primarily at 48 hours and stent placement to a smaller extent and MI to a smaller extent, and not death. There are very few deaths, and they are very balanced. So the components that contribute are repeat procedures and to a lesser extent MI. But that is for non-specified endpoints.

DR. PACKER: Okay. Any discussion? I do not

think so.

[No response.]

DR. PACKER: We have the same issues with respect to this trial in terms of the judgment. Again, A, B, C, D, E are the options. Dan, why don't you lead us off with your view on question eight?

DR. RODEN: Well, you know, Bob asked a question at the end of the RESTORE discussion before we broke for lunch to which he did not get an answer. I would have actually liked to hear that discussion a little bit. Maybe we could do that now. The question that Bob asked I think was what indication does RESTORE support or what does RESTORE support?

Because the primary, pre-specified endpoint is not met at 30 days, I do not find this as persuasive as the findings of a typical successful trial. I recognize all of the reasons why one might want to choose an endpoint earlier on. I think that the agency and all of the sponsors that are developing these drugs will have figured out that we are sort of teaching people as we go along to design the trials in such a way that there is a maximum likelihood that the prespecified endpoint gets met. So I do not think that it is probably attributable to the play of chance. I think that there is something in the data that says that there is a better outcome with the treatment group than the control

group. So I do not think that I would vote A. But because the primary pre-specified endpoint is not met, I cannot vote C, so that is why I would vote B. I would like to have some discussion on what this particular result adds to the portfolio. We are not going to have that discussion.

DR. PACKER: Right. We are not going to have that discussion because this question is looking at RESTORE in isolation.

DR. RODEN: Okay.

DR. PACKER: Okay. Can we have additional questions or comments? Shall we go directly to a vote?

PARTICIPANT: Vote.

DR. PACKER: Let's vote. Marv wants to lead us off. We will start at the other end. A, B, C, D, or E.

DR. KONSTAM: B.

PARTICIPANT: B.

PARTICIPANT: B.

PARTICIPANT: B.

PARTICIPANT: B.

PARTICIPANT: B.

PARTICIPANT: B.

PARTICIPANT: A.

PARTICIPANT: B.

PARTICIPANT: B.

DR. PACKER: Okay. Now, that actually brings us

to an interesting situation with question number nine because, as we have created a parallel between pursuit and PRISM-PLUS, the agency is now creating a parallel between RESTORE and Impact II. Please help me out here. If I remember correctly, these trials are not exactly the same kind of study.

PARTICIPANT: Page 361 has a summary.

DR. PACKER: Okay. These are not exactly the same kind of study, if I remember. Please help me if I am incorrect. Impact II was a trial of angioplasty patients, patients undergoing angioplasty. Whether or not they had unstable angina and this RESTORE is a trial of angioplasty only in patients who have been admitted for unstable angina, is that a valid distinction.

DR. LIPICKY: Well, not quite. The percentage of patients who basically had unstable angina and then had intervention because of that in the two trials is about the same. It is a little higher here than it was in Impact II, but it is not night and day. It is like, you know, a 10 percent difference or something on that order.

DR. PACKER: Well, it should be a hundred percent in RESTORE.

DR. LIPICKY: But it is not. There is a 10 percent difference between the two. I do not know whether RESTORE is a hundred percent of not.

DR. THADANI: Impact II was an angioplasty trial. It had nothing to do with Pursuit because that was the first trial presented to the committee last year. This was a low-dose/high-dose Integralin, and those were --

DR. LIPICKY: No, that is something else.

DR. THADANI: No, in the Impact II.

DR. PACKER: We are just talking about the patient populations recruited.

DR. THADANI: In the Restore there are also patients who have Q-wave MI and then they are also included. I am not sure if they were included in Impact II. They are also impacted.

DR. LIPICKY: We have the data if you want to listen to it. The criteria, the characteristics of the patients in the two trials, Impact II with Integralin, and RESTORE with Tirofiban, if you look through the demographics and the reasons why they are in the trial, they are almost identical. So there is not really a patient distinction criterion that drives you to say that these are two different patient populations studied.

DR. PACKER: Okay.

DR. LIPICKY: If you disagree, show the data. If you agree, then we do not have to talk about it anymore because the guy who knows the numbers and has the tables in his hand is saying that I described it properly.

DR. PACKER: Okay. Now, although the event rates are described in the question, although Impact II results were nominally significant, .041, let me remind everyone that the P value, critical P value for Impact II was .035, they are not statistically distinguishable. That is the treatment effect in one is statistically similar to the treatment effect in the other. The KI-square is .03.

Did RESTORE and Impact find the same phenomenon? If not, what was different? Dan?

DR. RODEN: I think the phenomenon that they found was a potential effect in patients undergoing intervention. I am not sure that I would go further than that. Remember, you quoted a value of .04 for statistical significance. For the low-dose group alone the published value in the Lancet article was .063. The nominal value is .03. So, no matter what way you cut it, Impact II, like RESTORE, did not meet its primary endpoint. So I am not sure what either of the trials showed. But to the extent that one believes that they showed a beneficial effect on outcome later. This is not a P-value question.

DR. RODEN: Right, okay. Well, I am just, well --

DR. LIPICKY: This is do you think that the phenomenon described by whatever you think the trial found --

DR. RODEN: Yes.

DR. LIPICKY: -- is the same phenomenon or not?

DR. RODEN: Whatever the phenomenon was, Ray, I think that it is the same thing.

DR. LIPICKY: Okay. That is the question.

DR. RODEN: Am I allowed to say what the phenomenon might have been? I think that I already said that.

DR. LIPICKY: You already said that yes.

DR. TEMPLE: Well, I am looking at the question more than I did before. I like it less. One of the things that both studies found was an effect early that met anybody's test for nominal statistical significance. I would appreciate it if while you consider all of this you tell us what you think about that. That was true both of Impact II and it was true of RESTORE. If you look early, you see low, nominal, significance, and, in some sense, the same phenomenon you see everywhere else you look.

DR. LINDENFELD: Didn't Impact have --

DR. TEMPLE: I would be interested in what you think about that.

DR. LINDENFELD: Didn't they have an advantage early because the study was started with the procedure? I think that impact had an advantage early because wasn't the study started at the time of procedure and a lot of the events were enzymes within the first two days?

DR. RODEN: The first dose of Tirofiban was given after that.

DR. LINDENFELD: No. I am talking about with Impact. In other words, that study started with the procedure so that a lot of the events were recorded early because they were enzyme events post-procedure.

DR. LIPICKY: There are a lot of differences between -- in the results of the trial and so on and so forth. The only thing this is asking is do you think these two trials with two different drugs sort of describe a phenomenon that is not -- only one person here said that restore was just the table of random numbers. Everyone else said that it was something other than that. So it describes something. The only question is do you think it describes something different from what was described by the Impact II trial? That was the question. That is all you need to address. There are lots of differences between the trials, lots of numbers that are different, et cetera, et cetera. It is just as -- you know, it was one study -- did one study describe a Guernsey cow and the other study describe a raging bull?

DR. RODEN: They both describe cows. But remember Impact II had two cows and they had to throw one of them out.

DR. LIPICKY: That is okay. I just wanted to know

if they both described cows.

DR. RODEN: Well, I think that the fact that we know what dose -- that the right dose was studied here as opposed to the other study does impact my interpretation of your question.

DR. DiMARCO: Ray, are you just asking do we think that a IIb/IIIa inhibitor is useful in the short-term around the time of angioplasty?

DR. PACKER: No. The question is are the results of these two trials suggest that there is a difference between these two drugs in this clinical situation? Is that a correct statement?

DR. LIPICKY: That is a correct statement.

DR. KONSTAM: I am going to take a shot at answering that question. It is a different sort of question than we are usually asked. It is sort of fun. I will answer it this way in saying that if you look at the entirety of the data and not worry too much about comparing individual P values, I think that the most likely explanation that I could come up with is that we are looking at the same thing, that is that it is the same set of events occurring in the same clinical situation with drugs that are in the same class. It looks pretty similar.

DR. LIPICKY: I think that the only people who have to talk are the people who would say something

different than that and explain why they think it is different.

DR. LINDENFELD: I think it might be a little bit different. I think that it is the same process of preventing thrombosis. I believe that in the first 48 hours impact were primarily procedurally-related events. Here the first 48 hours were generally prior to procedures in RESTORE; is that not right.

PARTICIPANT: No, no, no.

DR. LINDENFELD: I am sorry. That is wrong. I am sorry.

PARTICIPANT: She corrected herself.

DR. RODEN: The results of the low dose of Impact II and this trial I would agree with Marv say the same thing. So I should not say anything more. But I will continue to harp on the idea that high dose, relatively high dose Integralin in Impact II may not have shown the same thing. Now, whether that is because of a statistical fluke or some pharmacology that we do not know about, we do not know. But that is worth bearing in mind.

DR. THADANI: I think it is important to know when you say they are similar did you include the high-dose group too? Because what was disturbing in the Impact trial was that the low dose -- you would think that the particular phenomena is important. Nobody is denying that. The trend

was the same. It was not significant. So, if you compare it to the high dose you will find a different result. So you may say that a high dose is not effective and this is not effective. So I am not sure if this is included in that or are you only including low dose effects.

DR. PACKER: Let us be very careful here. In Impact II neither dose beat placebo at the pre-specified alpha.

DR. RODEN: No, the low dose did.

DR. PACKER: No. .04, .06 with the critical P of .035.

DR. RODEN: There are various P values that have been used and none of them are below .035 that is true, okay. Also, we probably do not agree that .035 was the right critical value. It is probably closer to .028. However, in the early endpoints both groups win easily.

DR. KONSTAM: That was the intent to treat result that you cited and that is an improper analysis. It should be treated as randomized. The treated as randomized which was a pre-specified analysis in fact made it as a statistically-significant thing, but that is okay. This is not the business of P values.

DR. PACKER: So now the question is Marv has proposed to the committee that these trials found the same thing if they found anything.

[Laughter.]

DR. PACKER: Who would disagree with that?

DR. THADANI: The last word.

DR. PACKER: Let us go on to number 10. No one would disagree.

How would you characterize the incidence and severity of bleeding in the Tirofiban trials? To what extent was the bleeding attributable to the concomitant use of aspirin plus heparin? Dan?

DR. RODEN: There is an increased incidence of bleeding with Tirofiban which runs counter to some of the more recent literature that suggests that these drugs may not actually have a variance increase. It is modest. It does not seem to be very serious. I cannot tell how much of it is due to concomitant aspirin and heparin. Although since the controls were aspirin and heparin largely, I think that some of it is attributable to drug or drug plus aspirin plus heparin.

DR. PACKER: Okay. And the first question characterize the incidence and severity of bleeding?

DR. RODEN: It has slightly increased over that in the control groups and the severity is -- well, it depends on your view of bleeding. I mean, if bleeding requires transfusion, then that probably puts it right into the severe category automatically. But I think that the

incidence was low enough and the severity was modest. I do not know what word you would want to use. It is not severe.

DR. PACKER: Jeff?

DR. BORER: Yes. I think that this question always has to be considered in a slightly different way than the way it is written. The incidence and severity of bleeding we can define from the books we have got. The question is that compared to the benefit that we perceive is this incidence of severity and bleeding acceptably low for the intended use. If you had asked me that question I would say that, yes, it is acceptably low for the intended use given what I perceive as the benefit here. So I agree with Dan, I think it is fine.

I also agree that there is, you know, that there certainly is some effect of the drug by itself given the study design structure, but we have no way of knowing since aspirin and heparin always were present whether there was any synergistic effect or not.

DR. PACKER: Does anyone disagree with the summary statements that Dan and Jeff have made?

DR. THADANI: I think that on page 247, if you look at it, the question is can you differentiate the aspirin/heparin effect? I think that you might have to look at the Tirofiban group alone in that group. Those people who did not have a procedure, there is a slight nuisance

bleeding.

PARTICIPANT: But they had aspirin.

DR. THADANI: Sure. But if you add this drug on its own there is a slight nuisance bleeding that is very procedure related, but not a major one. So I think that it is hard to separate completely aspirin and heparin. But I think that if you compare just one of them alone it tends to cause little -- slightly more bleeding which is consistence with all of the IIb/IIIa's. It is not unique to this but I think you can see that.

DR. PACKER: Marv.

DR. KONSTAM: I want to make a general point. It is not based on any hard data but just based on having sat here and reviewed these data sets on a number of these drugs and also from clinical experience that -- and I will just make this statement. I believe that the number of bleeding events with these agents is being under-reported. So I think that based on the data at hand that there is no doubt in my mind that the risk-benefit ratio here will not be strongly influenced by the number of bleeds reported. But, as we go forward with these agents, I think that that is something to keep our eye on. It is something a little bit less than oh this is a slam-dunk and I do not have to worry about bleeding in these cases.

DR. PACKER: Okay. Let's move forward to number

11. The division has routinely advised sponsors that refractory ischemia is so subjective that it is not the appropriate endpoint or an appropriate driving component of a combined endpoint for a trial meant to stand on its own. Should the division continue to give this advice? We have already explored extensively today the difficulties in the endpoint of refractory ischemia and that is something which the division would like us to know whether what we have heard today in the discussions which have taken place today should change their guidance in this matter.

DR. RODEN: I think that it is possible to make refractory ischemia a phenomenon that is not so subjective. Perhaps that was done in this trial in PRISM-PLUS. Under those conditions, I think that it is an appropriate endpoint. If it is included as an endpoint, then it runs the great risk that it will be the driving endpoint. There is no question. I guess that one way to answer this question is then for us to decide as people who take care of patients whether a reduction in the rate of refractory ischemia is an important clinical endpoint. My view would be that it would be.

DR. PACKER: Discussion?

PARTICIPANT: I agree.

DR. THADANI: I echo your view. I think that it is important. But, again, the management, when you are

looking after these patients vary. And PRISM-PLUS used a point to optimize the therapy because it is possible that you can have refractory ischemia and I could bump the nitroglycerine dose from 80 to 160 mics per minute and the pain goes away. And when I am on the unit that patient does not necessarily go to the cath lab. When my colleague might have a threshold lower he sends them to the cath lab. So I think that it is important. I am not denying that. But, again, unless you can come with a very consistent guideline -- and I think that they did that here. They tried to give a beta blocker for the heart rate and nitrates. It is useful, but one has to be very careful if this is the only driving force.

If you are getting an indication that it prevents ischemia that is fine. I mean, if you do a trial like that, there is nothing against it. We do it with stable angina. But if you are looking at the outcome, that is a different issue. So I think that that is a good surrogate endpoint. Whether it should be just a primary for one trial, I do not know.

DR. PACKER: Okay. First of all, it is not a surrogate.

DR. THADANI: Well, it is a composite endpoint.

DR. PACKER: No, no. There is no problem here with composite.

DR. THADANI: Okay.

DR. PACKER: The question here is one of hierarchy among clinically-relevant endpoints.

DR. THADANI: I think that, as a physician when you are looking at this work, because that is what is driving you. The patient comes to the hospital. Why does he come to the hospital? It is for chest pain. If you do an electrocardiogram, and he has got SD depression. So you are treating that as an episode. So, if you believe in that then obviously awarding that is a good thing. So I think that you have got to take that into algorithm because that is why you are looking after these patients because they come with chest pain. They have got electrocardiographic changes and you want to improve the final outcome. You know, we do not want to go into control CF silent ischemia here whether the treating is good or bad. That is a different issue.

But I think that when a patient is in the hospital, you are trying to prevent pain happening at 3:00 in the morning so that it triggers a coronary angiogram at that time. So it is a useful endpoint. Whether it stands alone that is a different issue.

DR. LIPICKY: Milton, I think that we are asking -- we make a very clear statement there. We say certain things. We are asking the committee to say should we

continue, that is a yes, or should we no longer say those things, that is a no. I think that we understand what both Udho has said and Dan has said. We are just asking for people to say yes or no. Depending on how that comes out we may try to figure it out. Okay? You do not have to explain it.

DR. PACKER: Okay. Let's not have anymore discussion. Let's have a vote. Marv?

DR. KONSTAM: I want to voice in favor of still discouraging this endpoint.

DR. PACKER: Okay. We are voting.

DR. KONSTAM: Okay.

DR. PACKER: We are going to vote.

PARTICIPANT: No. We need some explanation.

DR. KONSTAM: All right. So I will explain my vote as I go.

DR. PACKER: Okay.

DR. KONSTAM: All right?

DR. PACKER: Yes.

DR. KONSTAM: So what is the question?

[Laughter.]

DR. KONSTAM: Yes, the answer is yes. I guess that I agree with the things that Dan and Udho said. The difference though is I think that we are in the context of the way patients with unstable angina are managed in the

United States. In that context, there is such a high rate of advancement to intervention that the ability to distinguish this entity of refractory ischemia I think in that context gets very blurred. And so that if we were in a milieux in which there was a high rate of an attempt to manage patients medically indefinitely I think that it would be easier to utilize this. I think that in the context of the way that medicine is practiced here, I think that it is much more difficult. For that reason, I would tend to shy away from this as an endpoint.

DR. PACKER: Bob, do you want to clarify?

DR. TEMPLE: Well, a little bit. I think that the question overstates what we said slightly. We have discouraged use of that endpoint. I do not think that we have said forget it, no way. There are two reasons. One is that we are worried about how well-defined it can be. But when we tell somebody do not use the endpoint that we are worried about precision on, this is a for your own good advice. That is that we think that it is too noisy and you would do better to pick something else. However, whether you go on to an urgent intervention is fairly noisy and subjective also so that we are not totally sure that we have been guiding people toward a better endpoint.

There is another reason that I want to throw into the mix which is that when you have a combined endpoint you

would like the components to be of roughly equal weight. In other words, you would not want death, MI, and tension headache. That would seem stupid.

[Laughter.]

DR. TEMPLE: So, part of our feeling was that if this is so refractory and it is so awful it ought to result in something. You ought to get an MI, die, or have an intervention. And if it is not that then maybe it does not deserve to be in the same endpoint as death plus MI. I am not wedded to that view. I am just saying that that is to some extent why we tended to discourage that as a component. And all of the things that you are talking about where this is the thing that drives the whole thing kind of make that point more.

The one consequence of that is that if somebody just used that as a separate endpoint we would not have the same objection. It is combining them all. On the other hand, it is kind of silly to use that endpoint and then not point out that everybody died. So it is a very complicated question. If you do not get to a final answer on this, as I said, I am writing a memo to Ray saying that we ought to explore a lot of this stuff. So maybe we will have a workshop on that one of these days.

DR. PACKER: Ray, do you have any other comments?

DR. LIPICKY: Maybe just one more. That is that

we do tell people that if they have refractory ischemia as part of the combined endpoint that we may ask them to do two trials.

DR. TEMPLE: Not as persuasive as --

DR. LIPICKY: All right. It is not as --

DR. TEMPLE: -- because it is not as heavy and endpoint.

DR. LIPICKY: -- if it is irreversible. So it is more than a discouragement. We say that we do not like that as much. And so really but I think that it could be -- I just want to see how many yeses and noes there are.

DR. PACKER: Well, let's find out how many yeses and noes there are. Marv, I think that you are saying that they should continue to give this advice?

DR. KONSTAM: Yes.

DR. PACKER: Jeff?

DR. BORER: I think that this endpoint -- the use of the endpoint should be discouraged in favor of more precisely definable endpoints, but it should not be precluded. It should be defined as rigorously as possible in order to assure maximal obtainable clinical severity. So I suppose that that is a very qualified yes sort of. I am sorry, it is a qualified no. I have been corrected.

DR. PACKER: Maybe I could try to make this a little bit easier because I have a feeling that each member

of the committee is going to want to make certain specific distinctions. No?

[Discussion off record.]

DR. THADANI: JoAnn wants to make a comment first.

DR. PACKER: Okay, JoAnn.

DR. LINDENFELD: I would vote yes. I think that the committee should continue to give this advice. I think that it is sometimes a difficult endpoint to sort out unless it is really rigorously defined and even that is difficult.

DR. PACKER: Udho?

DR. THADANI: You heard my feelings earlier. I think that the fact that we are giving these patients who are hospitalized with unstable angina drugs which can cause bleeding, we are already believing that unstable angina is bad for you. So I think that I am not saying that that should be the only point. We should be more guiding them as to what is really refractory ischemia. If you define that, I think that the useful endpoint, in addition to obviously all of the other hard endpoints -- and, again, the hard endpoint is death. Again, MI depends on how you define that too. So I think that my answer would be, Jeff, no, we should not discourage them to use it, but I think that we have to be more careful how they use it.

DR. PACKER: Okay.

DR. DiMARCO: I think that I agree with Udho. I

do not like combining a frequent but hard-to-define endpoint that is reversible with easy-to-define, irreversible endpoints that are sort of at a much lower frequency. I think that it distorts the use of the composite endpoint. But I do think that control of chest pain can be a valuable endpoint. We do it in angina studies, why not in unstable angina studies? It just has to be very rigorously defined and checked. That is why I actually like the idea of having an events committee rather than the investigators defining it.

PARTICIPANT: That was a no?

PARTICIPANT: That was a no.

DR. RODEN: Jeff Borer said it better than I. I agree with his qualified no.

DR. MOYE: Yes, whole-heartedly. Please discourage these guys from doing this again.

DR. GRABOYS: Yes.

DR. PINA: Yes, unless there is a better definition or a better set of limitations.

DR. PACKER: Okay. I am voting yes as well. It is six to four. Let me just say that I am not exactly certain that there is a major distinction between those who voted yes and those who voted no.

[Laughter.]

DR. LIPICKY: I got that feeling. Believe it or

not that was useful. Okay. So it is okay.

DR. PACKER: Okay. Number 12. Should Tirofiban be approved for the treatment of patients with acute coronary syndrome? If so, what regimens should be recommended? Should Tirofiban be recommended for use as adjunct to therapy, as indifferent, alternative to heparin or preferable to heparin?

Let me just simply say that we need to make this simple. So we are going to go around once and we are going to go around several times. It would really be helpful if people could be very concise in their responses. If you think that Tirofiban should be approved for any indication under any conditions, with any qualifications, you just think that it should be approved for something, then the answer that you should be giving to this should be yes.

DR. RODEN: No, just acute coronary syndrome.

DR. PACKER: No, acute coronary syndrome. But this is not an invitation to wordsmith. Okay. Dan.

DR. RODEN: Well, this is actually not a very easy decision obviously. The standard would be two strikingly positive trials. In my view, PRISM-PLUS is one strikingly positive trial and the remainder of the data maybe add up to a second and maybe not. My inclination is to say that it should be approved for adjunctive therapy to heparin in acute coronary syndrome. And the regimen recommended is

that used in PRISM-PLUS with heparin which is 0.4 micrograms per kilogram per minute over 30 minutes followed by whatever the maintenance was, .01.

DR. PACKER: Okay. Let's go down the line. Ileana?

DR. PINA: I will make it simple. I agree with Dan.

DR. GRABOYS: I agree with Dan.

PARTICIPANT: Yes.

PARTICIPANT: Yes.

DR. GRABOYS: I agree. We both agree.

DR. PACKER: You get two yeses. Your turn.

DR. MOYE: I disagree. I do not think that this compound should be approved. I think that these scientists have displayed for us some very carefully-crafted trials. But I think that because of the endpoint composition and the timing that they used they sculpted their trials right out of clinical relevance from as far as I can see.

There are two issues. One is endpoint composition. In PRISM, as we mentioned before, the main effect for the primary endpoint for efficacy was seen in the weakest possible component of the primary -- of the endpoint. And there are endpoint timing issues that permeate all of these trials. I have a sufficient concern about findings of -- very strong findings early with the

lack of benefit, essentially indistinguishable from the control group at what I think was a reasonable time point, 30 days. So I have two issues, endpoint composition and endpoint timing. Frankly, I guess that I could live with one fly in the ointment but not two. So my vote is not to approve for any of the indications recommended today.

DR. PACKER: Dan has voted. John?

DR. DiMARCO: I vote to approve. I agree with what Dan said. I think that I would also, in situations where it was going to be initiated at the time of intervention that I would accept the RESTORE dosage schedule as an alternative to waiting for two days for the infusion to build up.

DR. PACKER: Udho?

DR. THADANI: This is one positive trial. If the agency approves the one positive trial then it is approvable on that basis with the provision that there is one positive trial. In contrast to what Don has said, I think that I would recommend the regimen used in the trial which is to days before and then do angioplasty. I am not seeing anything if you just do it straight-away because RESTORE we said did not show anything. So I think that if you are going to do that you should do infusion for two days, and then do an intervention. That is what the trial did. In other trials, the results are not the same way.

DR. PACKER: Let me just clarify. We did not say that RESTORE did not show anything. We said that it provided evidence.

DR. THADANI: Was not a positive trial at the primary endpoint.

DR. PACKER: No. We voted clearly that it was less persuasive than the single trial.

DR. THADANI: Yes, sure. Whatever.

DR. PACKER: Okay.

DR. THADANI: Than even a single trial.

DR. PACKER: The answer is yes. Bob, hold on one second. The answer is yes?

DR. THADANI: Yes. I would say yes with one positive trial results if that is what the regular decision is based on.

DR. PACKER: Okay. Now Bob.

DR. TEMPLE: Well, we just need to be clear. There are nominally two positive trials. Lem has expressed some doubt about the meaningfulness of one of the endpoints in one of them. I just want to be sure that this sort of question has some precedent value and things like that. I just want to be sure that I know what I am hearing.

There were on their face two trials that reached their primary endpoint. I understand that this question is about whether the endpoints are the right ones in one of the

trials and so on.

DR. THADANI: Normally we ask a question about two trials.

DR. TEMPLE: Are you discounting PRISM?

DR. THADANI: PRISM is discounted because was only -- not on top of heparin. So we cannot use that data at all on that.

PARTICIPANT: But it beat heparin.

DR. THADANI: I realize that, but it was given as a monotherapy compared to heparin if we are talking about combination therapy. So we are comparing apples to oranges.

DR. TEMPLE: The question actually has not reached that. Those are subsequent components of this question. It is a very good question.

DR. PACKER: Actually, we have every -- if I understand the way that Dan answered the question, he answered it in a very comprehensive fashion. He said that he would recommend it for approval, recommend it for approval on top of heparin and that the dosing regimen would be that the dosing regimen is centrally used in PRISM-PLUS. As I understand it, Ileana and Tom agreed with him. John, with a very slight modification agreed as well.

Udho?

DR. THADANI: I would just say the same as long as the PRISM-PLUS regimen is used and if we state one trial as

a positive trial that is fine.

DR. PACKER: Okay.

DR. THADANI: We cannot use PRISM or other trials with that.

DR. PACKER: But remember why Bob is asking the question. Because of your -- you have modified what everyone else has said with one clause, and that clause is that you would vote yes based on one positive trial. What Bob is concerned about, although he has not actually said this yet, is that you also voted that that one trial was as persuasive as one typical trial. This division does not generally like to make decisions based on the strength of one typical trial. So he wants to know how you can say that.

DR. THADANI: All I am just saying is that one trial beats the heparin which, again, Jeff alluded too as an active competitor, but is driven by the soft endpoints. If you believe in two trials, we do not have it, with one trial is it positive? Bob was asking me can you use PRISM? I do not think you can use PRISM data because that is monotherapy. So that is irrelevant.

DR. PACKER: Do you think that the data that you see is persuasive enough to you that the division should deviate from its usual principles on which it approves drugs?

DR. THADANI: Probably no. I do not think that they should deviate. Now, it is possible that with one trial which is positive and not only MI plus the soft endpoint and effects persist, so I think that if you look at that then one would have to say that this trial is positive for those endpoints.

Now, I think that in the past we have been asked different questions. Does that trial represent two trials. Even Dan when he qualified said that it is one trial. He never said that this was two trials when Dan qualified his remarks.

DR. PACKER: The question that Dan answered is not the question which is being asked right now. We have to -- as we have gone through this, you have specifically clarified, Udho, the fact that your decision -- no one else made this statement -- your decision was based on one trial. So, Bob wants to know why you think that that is good enough.

DR. THADANI: Well, I have not heard anything else, how anybody else could make a decision on any more trials because that is the only positive trial that we have had for combination arm. So how other people are making a decision on what? Because the first trial is just Tirofiban limb. There is no heparin limb, so you can forget that. On the RESTORE the primary endpoint is negative so that we have

just one trial. I want to hear other committee members, how they are saying that they are taking a composite endpoint. Maybe Dan wants to say something on that.

DR. PACKER: Let's take Udho's point and broaden it a little bit further. I think that the committee has in its deliberations of the individual trials said that there is one trial which is as persuasive as a typical trial and there are two trials which are less persuasive than a typical trial. If one looks at the usual decision-making process and looks for two trials, then at a pure technical level, and I want to emphasize that, we have not said that there are two trials. So there is the -- is the committee recommending yes because it considers two trials that are less persuasive than a single trial but have some persuasive power together with everything that they see in this database? Does that add up to a second persuasive finding? I hate to use the word trial because, you know, basically, is there sufficient confirmation in the database to allow you to conclude that the totality of the strength of the evidence across three studies is equivalent to what one would generally see in two positive trials? This is essentially what this is really all about.

In other words, we said that one trial is good, a typical trial. One trial is less than typical, one is -- another is less than typical. I got the impression from the

yeses that --

DR. TEMPLE: That was a divided vote.

DR. PACKER: What is that?

DR. TEMPLE: It was six to four on PRISM.

DR. PACKER: Six to four. Right.

DR. THADANI: I think that the other issue is if you look at the PRISM-PLUS trial, you cannot combine the three trials. You only can talk about two. Because in PRISM I one of the limbs was dropped which was used in PRISM. So I think that if you exclude that, there were two trials. I think that we should be able to ask a fair question. You should phrase it for RESTORE-PLUS, PRISM-PLUS.

DR. PACKER: What the division wants to know --

DR. THADANI: It is a complicated question.

DR. PACKER: -- what the division wants to know is not complicated. What the division wants to know is whether you think that based on the totality of the evidence provided to the committee which is essentially three trials whether you think that the totality of that evidence is as persuasive as the evidence that would be provided by two typical trials. Remember that we did it in isolation. The essence of this question is to do it all together. That is the basis for approval. If it is not the basis for approval but you still want to recommend approval, then you had

better clarify why you would deviate from the usual guidance.

DR. THADANI: Other people have worked on two trials. I am not sure.

DR. PACKER: Okay.

DR. THADANI: Because what they agreed was what Dan said that one trial is positive and other people agreed.

DR. LIPICKY: I will look back to seeing the transcript. Because what I think I said, Udho, is that there is one persuasive trial and then there is another part of the package. That entire package together including the persuasive trial and all of the other data we have seen make me go towards approval. That is the message.

DR. PACKER: Dan, let me just then take what you have said since you are the primary reviewer and I want the committee to actually specifically vote on this. We can do it very quickly looking at the totality of the data however you want to calculate that. If you want to do one plus .8 plus .7, whatever you want to do, or if you do not want to do it that way, you want to use a whole different conceptual model. Is the totality of the evidence provided to the committee on Tirofiban the same as or as persuasive as that which would be typically seen in two typical -- in two trials that you feel very comfortable with? How many of you believe that the totality of the evidence -- just raise

hands? How many of you believe that the totality of the evidence -- is there a qualification?

PARTICIPANT: The qualification has to come because we are looking at question 12 now, and then there is question 13 and 14. So the thing that drives my answer to question 12 is PRISM-PLUS. I might have a different answer for the others because -- and then some other trial will be the core value and the rest is the periphery.

DR. PACKER: Okay. The data -- it is this question. Just by a show of hands how many of you believe that the totality of the data is equivalent -- totality across three trials or any other information that you have is equivalent to that typically seen in two trials that you are comfortable with?

[Show of hands.]

DR. PACKER: That is eight to two.

Okay. And, Lem, based on the fact that it is not equivalent to two trials, votes no, and, Udho, you are the only one who needs to provide an explanation.

DR. THADANI: My explanation is that I think that PRISM-I is a very positive trial. To me, if you believe that the endpoints are for death plus ischemia- driven, which I believe is a very positive trial, that is one strong trial as opposed to two. So I would put a qualifier there that is all.

DR. PACKER: Okay. We have to complete the vote. JoAnn, please vote on question 12. You have already explained the basis of a vote, but now you have to vote.

DR. LINDENFELD: All right. I would vote yes. I think that the one strong trial, and one trial's primary endpoint is positive. All of the data is consistent. The events outnumbered the adverse experience by a fair amount.

DR. PACKER: Jeff?

DR. BORER: I think that Tirofiban should be approved for treatment of patients with acute coronary syndrome. I think that the data meet a reasonable standard of reapplicability for a therapeutic effect with safety acceptable for the intended use. I think that the regimen that should be recommended is that which was used in PRISM-PLUS and that, therefore, Tirofiban should be recommended for use as an adjunct to heparin plus aspirin which we left out.

DR. PACKER: Marv?

DR. KONSTAM: I agree with just pretty much the way that Jeff said. I just wanted to say that, in contradistinction to I think Udho's construct, I find PRISM-PLUS and extremely convincing trial and the data contained in aggregate between PRISM and RESTORE more than enough for the usual amount of confirmation that you need and that adds up to a yes vote.

DR. PACKER: Marv, I think that that is fine, but please realize that when you voted on PRISM-PLUS you said that it was the equivalent to a typical trial.

DR. KONSTAM: I would like to change my vote.

DR. PACKER: Okay.

DR. KONSTAM: I will go to D. I knew you were going to say that, Milton. I will make that a D.

DR. PACKER: Good. 13. Should Tirofiban be approved for -- before we even do that, the vote on approval is nine to one.

The vote on the reasons for approval, which is a database equivalent to two typical trials is eight to two. Ray and Bob, are any additional clarifications needed on this issue?

PARTICIPANT: Are you going to ignore Tirofiban alone?

DR. PACKER: No. We should consider that.

PARTICIPANT: I think you should.

DR. PACKER: Okay. Should Tirofiban -- let's just ask people should Tirofiban alone be approved for anything?

PARTICIPANT: Tirofiban plus aspirin.

DR. PACKER: Tirofiban plus aspirin on top of conventional therapy be approved for anything? That is actually part of question 12.

DR. THADANI: You cannot say conventional. The

conventional therapy includes heparin. You have to specify just aspirin.

DR. PACKER: This is taking Jeff's guidance and putting aspirin into the labeling. Does anyone on the committee think just by a show of hands -- anyone think that Tirofiban should be approved in the absence of heparin?

[Show of hands.]

DR. PACKER: The answer is nine to zero no, 10 to zero no.

Are there any clarifications on 12? Bob? Any other clarifications on 12?

DR. THADANI: On 12 I think that one of the other things that I would like to say -- I brought up the issue of non-steroidal and so did Jeff. I do not think that the non-steroidals were allowed during the trial. The reason that I am even mentioning that is that there is a nuisance bleeding. If you give nonsteroidal, you might increase the bleeding. So I just want to put some clarification that at least the way I read it non steroidals were helpful during the infusion time period.

Since the PRISM-PLUS is the one that we are recommending which is two days before, and for at least a longer period of time, we probably should caution people not to use the non-steroidal during that time period.

DR. PACKER: Okay. Bob Temple, any other

clarifications on either the vote or the rationale for the vote for 12?

DR. TEMPLE: No.

DR. PACKER: Okay. 13. Sponsor is --

PARTICIPANT: A subset of 12. It was a back-up for 12.

DR. PACKER: No. 13 cannot be skipped. It is a whole different issue.

PARTICIPANT: For everybody?

DR. PACKER: No, it did not say that. There is a specific incremental question in 13. The sponsor is specifically asking for mention in their labeling that says I think it is, including patients undergoing cardiovascular procedures. I am not going to read the whole thing. The committee has said unstable angina is -- acute coronary syndrome is okay. The sponsor wants not only acute coronary syndrome, it wants acute coronary syndrome including those about to undergo a cardiovascular procedure. We need to talk about that.

DR. TEMPLE: But what Bob says is true. If it is for everybody with acute coronary syndrome, it covers those who are about to undergo it, doesn't it?

DR. PACKER: That is true, but the medical --

DR. TEMPLE: Let's go ahead and discuss it.

DR. PACKER: -- Bob, the medial reviewer official

recommendation was to not allow that clause.

DR. BORER: No. I do not think that that was the -- I thought that the medical reviewer's point was that absent acute coronary syndrome that there was no basis for approving the drug for people who are just undergoing PTCA I believe. Isn't that right?

DR. PACKER: Could the reviewer clarify what was the intent?

DR. CHEN: I think that there is only one indication. My view of restore and the PDC subgroup is that they are a subgroup. My recommendation is based on PRISM-PLUS. That is a whole acute coronary syndrome patient. Whether it is approved for procedure subgroup cannot be supported by this data.

DR. BORER: Procedure without acute coronary syndrome, is that --

DR. CHEN: No, no.

DR. THADANI: I think that it is going on RESTORE trial you were saying is not positive.

DR. CHEN: No. All of the patients with the acute coronary syndrome should be approved. Whether you undergo a procedure of revascularization or not cannot be sustained by the specific data for an individual plan.

DR. PACKER: Jeff, that means that my interpretation of what the reviewer said the reviewer is

actually reaffirming.

DR. BORER: I do not understand.

DR. LIPICKY: That is okay. Look, there is a logical -- a potential logical inconsistency. You could say that people who are supposed to get PTCA should not receive this drug based on restore. Then I think that you have to explain yourself as to why you think that it is okay for people who are going to get PTCA but have acute coronary syndrome to get the drug because the distinction is pretty subtle. That is the reason that the question is in there.

DR. PACKER: Is this the question that the division still wants the committee to address or it can they settle this in direct discussions with the company based on their own sense of judgment? Do you need specific recommendations and guidance in this matter?

PARTICIPANT: No.

DR. PACKER: Number 14. Should Tirofiban be approved for the treatment of all patients who are about to undergo PTCA, this means with or without unstable angina? The rest of is self-evident. We will take a formal vote. We will just start with Ileana. Yes or no.

[There was voice vote and the motion was denied unanimously.]

DR. PACKER: Ray, Bob, any other questions that you have for us?

DR. TEMPLE: I just want to be sure that I understand. So the fatal flaw in this is the stupidity of having chosen the 30-day endpoint.

PARTICIPANT: In RESTORE.

DR. TEMPLE: At the short endpoint in RESTORE.

PARTICIPANT: That is correct.

DR. TEMPLE: In the short endpoint it looks like every other trial.

PARTICIPANT: Right. That is exactly what the committee is saying.

DR. TEMPLE: That is not a bad reason necessarily. I just want to be sure that I understand it.

DR. BORER: But people in RESTORE had acute coronary --

DR. TEMPLE: Only some did.

DR. THADANI: All of them did.

DR. TEMPLE: They had acute coronary problems. This is asking about anybody. Let me understand. You are saying the RESTORE population --

DR. PACKER: Since this meeting is not adjourned, we have to make sure that what we are not doing is engaging in sidebar chatter. Let's make sure that this is on this record.

DR. TEMPLE: In RESTORE people may well have had acute coronary syndromes, but they only got therapy at the

time or shortly before they were going to PTCA. So that is a different environment from the 48 hours that precede the fact that some people got procedures. Was the vote just now that it is okay to think of people -- of treating people like that in restore or not?

DR. PACKER: Dan?

DR. RODEN: I wanted to say something earlier about the issue of PTCA. As I look at the totality of the data, it seems to me that the strong data is PRISM-PLUS and it might be worthwhile to say something in the labeling that said whether patients went on to get PTCA or not, there does not seem to be any particular benefit or downside to that. The major effect is in identifying the patients who have unstable coronary syndromes and treating them. Does that make sense? So that it is not -- it is a little bit different from a drug where you might say that the indication is that somebody with an unstable coronary syndrome who is definitely going to have an intervention. Because I think that the data are that the benefit is in the unstable coronary syndrome. Whether patients get PTCA or not, the way that the data stand, I am not sure that we can say much that that is a beneficial thing on top of it.

DR. THADANI: I think that it is important to emphasize that because in the PRISM-PLUS, I said and Jeff said very clearly that infusion was given for two days.

Only then the whole data is driven by that trial. What you are asking is if a patient is going for a primary angioplasty and you give that IIb/IIIa at the time of angioplasty and that data is not positive on the primary event. I buy your point, but the 30-day endpoint was known.

DR. PACKER: Okay. I just want to be clear. It is not --

DR. THADANI: So we are saying use the PRISM.

DR. PACKER: Okay.

DR. THADANI: And if a patient needs angioplasty you could go ahead and do that.

DR. PACKER: I just wanted to be sure. If they had the since to chose a seven-day endpoint, they would have won big. The rest of the data do not matter. I just want to be sure.

PARTICIPANT: That was the reason -- I will disagree with the rest of the committee then. That was the reason why I said that we should accept that dosage from RESTORE. Because if the seven-day endpoint looks the same as PRISM-PLUS, and it is logically consistent that there are a lot of people who are not going to wait two days, so we had better give them a regimen that is applicable to the clinical situation.

PARTICIPANT: The pharmacology is that you do not have to wait two days. I mean, the drug, once it is in you

ought to get platelet inhibition anyway.

DR. LINDENFELD: The onset was fast even in the other bolus.

PARTICIPANT: So I do not think you need to worry about that.

DR. PACKER: Bob?

DR. TEMPLE: I think that basically the take-home point for most of the committee is that if they did not make their primary endpoint they do not get credit.

DR. PACKER: That is the take-home message this time. That is not the take-home message with Carvatalaw and stuff. I am not sure that I understand all of the distinctions. I am going to work on it.

PARTICIPANT: You really know how to hurt a guy. Your turn.

[Whereupon, the meeting was adjourned at 2:05 p.m.]

PAGESAVER KEYWORD INDEX - SINGLE FILE INDEX

84th Meeting
Cardiovascular and Renal
Drugs Advisory Committee

Second Day of Proceedings

DATE(s): Friday, April 10, 1998

COMMENTS: WORD (1) {3,15} = Keyword (number of occurrences) {page,line number}

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